

U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE FORM PTO-1390 (REV. 11-2000)		ATTORNEY'S DOCKET NUMBER 5940-01-SMH
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 CFR 15, <b>09/889106</b>
INTERNATIONAL APPLICATION NO. PCT/US99/30491	INTERNATIONAL FILING DATE 21 Dec 1999	PRIORITY DATE CLAIMED 13 January 1999
TITLE OF INVENTION 4' Heteroaryl Diarylamines		
APPLICANT(S) FOR DO/EO/US BARRETT, Stephen Douglas; TECLE, Haile		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
<ol style="list-style-type: none"> <li><input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li><input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li><input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.</li> <li><input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</li> <li><input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))             <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input type="checkbox"/> has been communicated by the International Bureau.</li> <li>c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li><input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).             <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> is attached hereto.</li> <li>b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4).</li> </ol> </li> <li><input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))             <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input type="checkbox"/> have been communicated by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li><input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li><input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</li> <li><input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</li> </ol>		
Items 11 to 20 below concern document(s) or information included:		
<ol style="list-style-type: none"> <li>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>13. <input type="checkbox"/> A <b>FIRST</b> preliminary amendment.</li> <li>14. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li>15. <input type="checkbox"/> A substitute specification.</li> <li>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</li> <li>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</li> <li>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</li> <li>20. <input checked="" type="checkbox"/> Other items or information:             <ul style="list-style-type: none"> <li>International Search Report (PCT/ISA/210)</li> <li>International Preliminary Examination Report (PCT/IPEA/409)</li> <li>Associate Power of Attorney Or Agent (37 CFR 1.34)</li> <li>Certificate of Mailing by Express Mail</li> </ul> </li> </ol>		

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PD-5940-01-SMH

U.S. APPLICATION NO. (If known) 37 CFR 1.5

INTERNATIONAL APPLICATION NO.  
PCT/US99/30491ATTORNEY'S DOCKET NUMBER  
5940-01-SMH21.  The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1000.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$860.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$710.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$690.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$100.00

**ENTER APPROPRIATE BASIC FEE AMOUNT =****CALCULATIONS PTO USE ONLY**Surcharge of \$130.00 for furnishing the oath or declaration later than  20  30 months from the earliest claimed priority date (37 CFR 1.492(e)).

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$
Total claims	50 - 20 =	30	x \$18.00	\$ 540.00
Independent claims	1 - 3 =		x \$80.00	\$ 0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$270.00	\$
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$ 1,400.00
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+ \$	
<b>SUBTOTAL =</b>				\$
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			\$	
<b>TOTAL NATIONAL FEE =</b>				\$ 1,400.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property			+ \$	
<b>TOTAL FEES ENCLOSED =</b>				\$ 1,400.00
				Amount to be refunded: \$
				charged: \$

- A check in the amount of \$ \_\_\_\_\_ to cover the above fees is enclosed.
- Please charge my Deposit Account No. 23-0455 in the amount of \$ 1,400.00 to cover the above fees. A duplicate copy of this sheet is enclosed.
- The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0455. A duplicate copy of this sheet is enclosed.
- Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.**

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09/889106

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## CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)

Applicant(s): Stephen Douglas Barrett, et al.

Docket No.

5940-01-SMH

Serial No.

Filing Date

Examiner

Group Art

Invention:

4' Heteroaryl Diarylamines

I hereby certify that this

Patent Application for filing under 35 U.S.C. 371

(Identify type of correspondence)

Is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under

37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231

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## 4' HETEROARYL DIARYLAMINES

This invention relates to 4' heteroaryl diarylamines having pharmaceutical  
5 activity.

### BACKGROUND

MEK enzymes are dual specificity kinases involved in, for example, immunomodulation, inflammation, and proliferative diseases such as cancer and  
10 restenosis.

Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins. Defects include a change either in the intrinsic activity or in the cellular concentration of one or more signaling proteins in the signaling cascade. The cell may produce a  
15 growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common mutations occur in genes encoding the protein known as Ras, a G-protein that is activated when bound to GTP, and inactivated when bound to  
20 GDP. The above-mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in most cell types. Defects in this signaling system, especially in the deactivation of the Ras-GTP complex, are common in cancers, and lead to the  
25 signaling cascade below Ras being chronically activated.

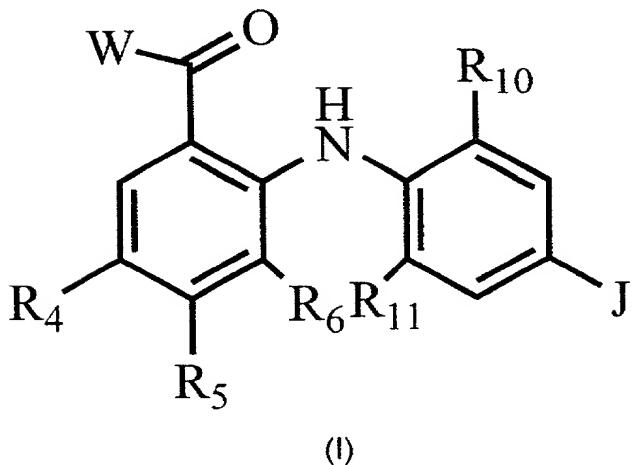
Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active Ras-GTP for its own activation is the Raf family. These in turn activate MEK (e.g., MEK<sub>1</sub> and MEK<sub>2</sub>) which then activates MAP kinase, ERK (ERK<sub>1</sub> and  
30 ERK<sub>2</sub>). Activation of MAP kinase by mitogens appears to be essential for proliferation; constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, for example by use of a

dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of Raf and other kinases, most likely through a phosphorylation mechanism. Once activated, Raf 5 and other kinases phosphorylate MEK on two closely adjacent serine residues, S<sup>218</sup> and S<sup>222</sup> in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates MAP kinase on both a tyrosine, Y<sup>185</sup>, and a threonine residue, T<sup>183</sup>, separated by a single amino acid. This double phosphorylation activates MAP kinase at least 100-fold. Activated MAP 10 kinase can then catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases. Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, such as a kinase, a transcription factor, or another cellular protein. In addition to Raf-1 and MEKK, other kinases activate MEK, and MEK itself appears to be a signal 15 integrating kinase. Current understanding is that MEK is highly specific for the phosphorylation of MAP kinase. In fact, no substrate for MEK other than the MAP kinase, ERK, has been demonstrated to date and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or even phosphorylate denatured MAP kinase. MEK also appears to associate 20 strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating 25 through allosteric mechanisms rather than through the usual blockade of the ATP binding site, may be found.

SUMMARY OF THE INVENTION

The invention features a compound having the formula (I) below:

5



In formula (I), W is  $OR_1$ ,  $NR_2OR_1$ ,  $NR_AR_B$ ,  $NR_2NR_AR_B$ ,  $O(CH_2)_{1-4}NR_AR_B$ , or  
10  $NR_2(CH_2)_{1-4}NR_AR_B$ .  $R_1$  is H, C <sub>1-8</sub> alkyl, C <sub>3-8</sub> alkenyl, C <sub>3-8</sub> alkynyl,  
C <sub>3-8</sub> cycloalkyl, phenyl, (phenyl)C <sub>1-4</sub> alkyl, (phenyl)C <sub>3-4</sub> alkenyl, (phenyl)-  
C <sub>3-4</sub> alkynyl, (C <sub>3-8</sub> cycloalkyl)C <sub>1-4</sub> alkyl, (C <sub>3-8</sub> cycloalkyl)C <sub>3-4</sub> alkenyl,  
(C <sub>3-8</sub> cycloalkyl)C <sub>3-4</sub> alkynyl, C <sub>3-8</sub> heterocyclic radical, (C <sub>3-8</sub> heterocyclic  
radical)C <sub>1-4</sub> alkyl, (C <sub>3-8</sub> heterocyclic radical)C <sub>3-4</sub> alkenyl, or (C <sub>3-8</sub> heterocyclic  
radical)C <sub>3-4</sub> alkynyl. Each of  $R_2$  and  $R_3$  is independently H, phenyl, C <sub>1-4</sub> alkyl,  
C <sub>3-8</sub> alkenyl, C <sub>3-8</sub> alkynyl, C <sub>3-8</sub> cycloalkyl, or (C <sub>3-8</sub> cycloalkyl)C <sub>1-4</sub> alkyl. Each of  
15  $R_4$ ,  $R_5$  and  $R_6$  is independently H, F, Br, Cl, or  $NO_2$ .  $R_A$  is H, C <sub>1-6</sub> alkyl, C <sub>3-8</sub>  
alkenyl, C <sub>3-8</sub> alkynyl, C <sub>3-8</sub> cycloalkyl, phenyl, (C <sub>3-8</sub> cycloalkyl)C <sub>1-4</sub> alkyl, (C <sub>3-8</sub>  
cycloalkyl)C <sub>3-4</sub> alkenyl, (C <sub>3-8</sub> cycloalkyl)C <sub>3-4</sub> alkynyl, C <sub>3-8</sub> heterocyclic radical,  
20 (C <sub>3-8</sub> heterocyclic radical)C <sub>1-4</sub> alkyl, (aminosulfonyl)phenyl, (aminosulfonyl)-  
phenyl]C <sub>1-4</sub> alkyl, (aminosulfonyl)C <sub>1-6</sub> alkyl, (aminosulfonyl)C <sub>3-6</sub> cycloalkyl, or  
[(aminosulfonyl)C <sub>3-6</sub> cycloalkyl]C <sub>1-4</sub> alkyl.  $R_B$  is H, C <sub>1-8</sub> alkyl, C <sub>3-8</sub> alkenyl, C <sub>3-8</sub>  
alkynyl, C <sub>3-8</sub> cycloalkyl, or phenyl. J is  $SR_C$ ,  $OR_C$ ,  $SO_2R_C$ ,  $SOR_C$ ,  $SO_2NR_DR_E$ , C

1-8 alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, C<sub>5-8</sub> cycloalkenyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)-C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical (e.g., 1,2,5-thiadiazol-3-yl), (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, -M'E'G', (heterocyclic radical)-M'E'G', or (cycloalkyl)-M'E'G'. M' is O, SO, SO<sub>2</sub>, NR<sub>E</sub>, (CO)NR<sub>E</sub>, NR<sub>E</sub>(CO), SO<sub>2</sub>NR<sub>E</sub>, NR<sub>E</sub>SO<sub>2</sub>, or CH<sub>2</sub>. E' is absent (in other words, a covalent bond), (CH<sub>2</sub>)<sub>1-4</sub> or (CH<sub>2</sub>)<sub>m</sub>O(CH<sub>2</sub>)<sub>p</sub> where 1 ≤ (each of m and p independently) ≤ 3 and 2 ≤ (m + p) ≤ 4. G' is OR<sub>3</sub>, SOR<sub>C</sub>, SO<sub>2</sub>R<sub>C</sub>, or NR<sub>F</sub>R<sub>G</sub>; provided that where p = 1, then G' is H. Each of R<sub>C</sub>, R<sub>D</sub>, R<sub>E</sub>, R<sub>F</sub> and R<sub>G</sub> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> heterocyclic radical, and phenyl; NR<sub>F</sub>R<sub>G</sub> and NR<sub>D</sub>R<sub>E</sub> can each also independently be selected from morpholinyl, pyrazinyl, piperazinyl, pyrrolidinyl, or piperadinyl. R<sub>10</sub> is H, C<sub>1-4</sub> alkyl, halo, NO<sub>2</sub>, or SO<sub>2</sub>NR<sub>H</sub>R<sub>I</sub>. R<sub>11</sub> is H, halo, or NO<sub>2</sub>.

Each hydrocarbon radical or heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, phenyl, hydroxy, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxy, amino, and NO<sub>2</sub>. The invention also encompasses a pharmaceutically acceptable salt or C<sub>1-7</sub> ester of a compound of formula (I).

The invention also relates to a pharmaceutical composition including (a) a compound of formula (I) and (b) a pharmaceutically-acceptable carrier.

The invention further relates to a method for treating proliferative diseases, such as cancer, restenosis, psoriasis, autoimmune disease, and atherosclerosis. Other aspects of the invention include methods for treating MEK-related (including ras-related) cancers, whether solid or hematopoietic. Examples of cancers include colorectal, cervical, breast, ovarian, brain, acute leukemia, gastric, non-small cell lung, pancreatic, prostatic, and renal cancers. Further aspects of the invention include methods for treating or reducing the symptoms of xenograft (cell(s), limb, skin, organ or bone marrow transplant) rejection, osteoarthritis, rheumatoid arthritis, cystic fibrosis, complications of diabetes

(including diabetic retinopathy and diabetic nephropathy), hepatomegaly, cardiomegaly, stroke (such as acute focal ischemic stroke and global cerebral ischemia), heart failure, septic shock, asthma, and Alzheimer's disease.

Compounds of the invention are also useful as antiviral agents for treating viral infections such as HIV, hepatitis (B) virus (HBV), human papilloma virus (HPV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). These methods include the step of administering to a patient in need of such treatment, or suffering from such a disease or condition, a pharmaceutically-effective amount of a disclosed compound or pharmaceutical composition thereof.

10 The invention also features methods of combination therapy, such as a method for treating cancer, wherein the method further includes providing radiation therapy or chemotherapy, for example, with mitotic inhibitors such as a taxane or a vinca alkaloid. Examples of mitotic inhibitors include paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine. Other therapeutic 15 combinations include a MEK inhibitor of the invention and an anticancer agent such as cisplatin, 5-fluoro-2-4(1H,3H)-pyrimidinedione (5FU), flutamide, and gemcitabine.

20 The chemotherapy or radiation therapy may be administered before, concurrently, or after the administration of a disclosed compound according to the needs of the patient.

The invention further includes synthetic intermediates and methods disclosed herein.

Other aspects of the invention are provided in the description, examples, and claims below.

25

#### DETAILED DESCRIPTION

The invention features 4-heteroaryl diarylamine compounds, pharmaceutical compositions thereof, and methods of using such compounds and compositions.

30 According to one aspect of the invention, the compounds are MEK inhibitors. MEK inhibition assays include the in vitro MEK/MAP described at column 6, line 36 to column 7, line 4 of U.S. Patent Number 5,525,625 and the in

vitro MEK assay described at column 7, lines 4-27 of the same patent, the entire disclosure of which is incorporated by reference (see also Examples 13 et seq.). A whole cell assay is described in Example 16.

## 5 A. Terms

Certain terms are defined below and by their usage throughout this disclosure.

Alkyl groups include aliphatic (i.e., hydrocarbyl or hydrocarbon radical structures containing hydrogen and carbon atoms) with a free valence. Alkyl

10 groups are understood to include straight chain and branched structures.

Examples include methyl, ethyl, propyl, isopropyl, butyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, 2,3-dimethylpropyl, hexyl, 2,3-dimethylhexyl, 1,1-dimethylpentyl, heptyl, and octyl. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl.

15 Alkyl groups can be substituted with 1, 2, 3 or more substituents which are independently selected from halo (fluoro, chloro, bromo, or iodo), hydroxy, amino, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, arylalkyloxy, heterocyclic radical, and (heterocyclic radical)oxy. Specific examples include fluoromethyl, hydroxyethyl, 2,3-dihydroxyethyl, (2- or 3-furanyl)methyl, 20 cyclopropylmethyl, benzyloxyethyl, (3-pyridinyl)methyl, (2- or 3-furanyl)methyl, (2-thienyl)ethyl, hydroxypropyl, aminocyclohexyl, 2-dimethylaminobutyl, methoxymethyl, N-pyridinylethyl, diethylaminoethyl, and cyclobutylmethyl.

Alkenyl groups are analogous to alkyl groups, but have at least one double bond (two adjacent  $sp^2$  carbon atoms). Depending on the placement of a double 25 bond and substituents, if any, the geometry of the double bond may be *entgegen* (E), or *zusammen* (Z), *cis*, or *trans*. Similarly, alkynyl groups have at least one triple bond (two adjacent  $sp$  carbon atoms). Unsaturated alkenyl or alkynyl groups may have one or more double or triple bonds, respectively, or a mixture thereof; like alkyl groups, unsaturated groups may be straight chain or branched, 30 and they may be substituted as described both above for alkyl groups and throughout the disclosure by example. Examples of alkenyls, alkynyls, and substituted forms include cis-2-butenyl, trans-2-butenyl, 3-butynyl, 3-phenyl-2-

propynyl, 3-(2'-fluorophenyl)-2-propynyl, 3-methyl(5-phenyl)-4-pentynyl, 2-hydroxy-2-propynyl, 2-methyl-2-propynyl, 2-propenyl, 4-hydroxy-3-butynyl, 3-(3-fluorophenyl)-2-propynyl, and 2-methyl-2-propenyl. In formula (I), alkenyls and alkynyls can be C<sub>2-4</sub> or C<sub>2-8</sub>, for example, and are preferably C<sub>3-4</sub> or C<sub>3-8</sub>.

5 More general forms of substituted hydrocarbon radicals include hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, and corresponding forms for the prefixes amino-, halo- (e.g., fluoro-, chloro-, or bromo-), nitro-, alkyl-, phenyl-, cycloalkyl- and so on, or combinations of substituents. According to formula (I), therefore, substituted alkyls include

10 hydroxyalkyl, aminoalkyl, nitroalkyl, haloalkyl, alkylalkyl (branched alkyls, such as methylpentyl), (cycloalkyl)alkyl, phenylalkyl, alkoxy, alkylaminoalkyl, dialkylaminoalkyl, arylalkyl, aryloxyalkyl, arylalkyloxyalkyl, (heterocyclic radical)alkyl, and (heterocyclic radical)oxyalkyl. R<sub>1</sub> thus includes hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, aminoalkyl,

15 aminoalkenyl, aminoalkynyl, aminocycloalkyl, aminoaryl, alkylalkenyl, (alkylaryl)alkyl, (haloaryl)alkyl, (hydroxyaryl)alkynyl, and so forth. Similarly, R<sub>A</sub> includes hydroxyalkyl and aminoaryl, and R<sub>B</sub> includes hydroxyalkyl, aminoalkyl, and hydroxyalkyl(heterocyclic radical)alkyl.

Heterocyclic radicals, which include but are not limited to heteroaryls, include: furyl, oxazolyl, isoxazolyl, thiophenyl, thiazolyl, pyrrolyl, imidazolyl, 1,3,4-triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, indolyl, 1,2,5-thiadiazolyl and their nonaromatic counterparts. Further examples of heterocyclic radicals include piperidyl, quinolyl, isothiazolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuryl, tetrahydropyrrolyl, pyrrolidinyl, octahydroindolyl, thiadiazolyl, 25 octahydrobenzothiophenyl, and octahydrobenzofuranyl.

Selective MEK 1 or MEK 2 inhibitors are those compounds which inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an IC<sub>50</sub> for MEK 1 or MEK 2 that is at least one-fiftieth (1/50) that of its IC<sub>50</sub> for one of the above-named other enzymes. Preferably, a selective inhibitor has an IC<sub>50</sub> that is at least 1/100, more preferably 1/500, and even more preferably

1/1000, 1/5000, or less than that of its IC<sub>50</sub> or one or more of the above-named enzymes.

## B. Compounds

5 One aspect of the invention features disclosed compounds shown in formula (I) in the Summary section. Embodiments of the invention include compounds wherein: (a) R<sub>C</sub> is C<sub>1-2</sub> alkyl; (b) W is OH, or W is NHOR<sub>1</sub>; (c) R<sub>10</sub> is methyl or chloro; (d) R<sub>11</sub> is fluoro; (e) R<sub>11</sub> is H; (f) J is trihalomethyl or methylthio; (g) J is SO<sub>2</sub>CH<sub>3</sub>; (h) J is SOCH<sub>3</sub>; (i) J is C<sub>3-8</sub> alkynyl where the triple bond is between the carbon atoms alpha and beta to the phenyl group; (j) R<sub>1</sub> has at least one hydroxy substituent; (k) R<sub>1</sub> is H, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, phenethyl, allyl, C<sub>3-5</sub> alkenyl, C<sub>3-5</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, (C<sub>3-5</sub> cycloalkyl)C<sub>1-2</sub> alkyl, or (C<sub>3-5</sub> heterocyclic radical)C<sub>1-2</sub> alkyl; (l) R<sub>1</sub> is H or (C<sub>3-4</sub> cycloalkyl)C<sub>1-2</sub> alkyl; (m) R<sub>2</sub> is H, methyl, C<sub>3-4</sub> alkynyl, C<sub>3-5</sub> cycloalkyl, or (C<sub>3-5</sub> cycloalkyl)methyl; (n) R<sub>A</sub> is H, methyl, ethyl, isobutyl, hydroxyethyl, hydroxypropyl, cyclopropylmethyl, cyclobutylmethyl, C<sub>3-4</sub> alkynyl, phenyl, 2-piperidin-1-yl-ethyl, 2,3-dihydroxy-propyl, 3-[4-(2-hydroxyethyl)-piperazin-1-yl]-propyl, 2-pyrrolidin-1-yl-ethyl, or 2-diethylamino-ethyl; and R<sub>B</sub> is H; or where R<sub>B</sub> is methyl and R<sub>A</sub> is phenyl; (o) each of R<sub>4</sub> and R<sub>6</sub> is H, and R<sub>5</sub> is F; (p) each of R<sub>4</sub>, 10 R<sub>5</sub>, and R<sub>6</sub> is F; (q) R<sub>5</sub> is F; (r) each R<sub>5</sub> and R<sub>6</sub> is F and R<sub>6</sub> is Br; (s) each R<sub>5</sub> and R<sub>6</sub> is F and R<sub>6</sub> is H; (t) J is 1,2,5-thiadiazol-3-yl; or a combination thereof.

15 Preferably, where one of R<sub>1</sub>, R<sub>2</sub>, R<sub>A</sub>, R<sub>B</sub>, R<sub>C</sub>, R<sub>D</sub>, R<sub>E</sub>, R<sub>F</sub>, and R<sub>G</sub>, for example, is an alkenyl or alkynyl group, its double or triple bond, respectively, is not adjacent the point of attachment. For example, where W is NR<sub>2</sub>OR<sub>1</sub>, R<sub>2</sub> is 20 preferably prop-2-ynyl, or but-2 or 3-enyl, and less preferably prop-1-ynyl or but-1-enyl.

25 Examples of compounds of formula (I) include: 4-fluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 2-(4-methanesulfinyl-2-methyl-phenylamino)-4-nitro-benzoic acid; 3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-

benzoic acid; 3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 2-(2-methyl-4-methylsulfanyl-phenylamino)-4-nitro-benzoic acid; 3,4,5-trifluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 4-fluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-  
5 2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4,5-trifluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 4-fluoro-2-(4-methane-  
sulfinyl-2-methyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; and  
10 2-(4-methanesulfonyl-2-methyl-phenylamino)-4-nitro-benzoic acid; and the corresponding hydroxamic acid or cyclopropylhydroxamic acid of each.

Preferred examples of compounds of formula (I) are : 4-Fluoro-2-(4-methanesulfanyl-phenylamino)-benzoic acid (1); 4-Fluoro-2-(4-methanesulfinyl-phenylamino)-benzoic acid (2); 4-Fluoro-2-(4-methanesulfonyl-phenylamino)-benzoic acid (3); 4-Fluoro-2-(2-methyl-4-trimethylsilanylethynyl-phenylamino)-benzoic acid (6); 4-Fluoro-2-(2-methyl-4-ethynyl-phenylamino)-benzoic acid (7). Biological data on these seven compounds is given on page 17; full characterization of the compounds - MP, NMR, MS, IR and CHN- is given on pages 28-31.

20 Additional preferred compounds include the following: (a) 5-Bromo-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 5-Bromo-N-cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzamide; (b) 5-Bromo-2-(4-ethynyl-Cl-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-Cl-methyl-phenylamino)-3,4-difluoro-benzamide; 2-(4-Ethynyl-Cl-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-Cl-methyl-phenylamino)-3,4,5-trifluoro-benzamide; 2-(4-Ethynyl-Cl-methyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 5-Bromo-N-cyclopropylmethoxy-2-(4-ethynyl-Cl-methyl-phenylamino)-3,4-difluoro-benzamide; (c) 5-bromo-3,4-difluoro-

2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; (d) 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; (e) N-cyclopropylmethoxy-3,4-difluoro-2-(4-imidazol-1-yl-2-methyl-phenylamino)-benzamide; (f) N-cyclopropylmethoxy-3,4,5-trifluoro-2-(2-methyl-4-[1,2,5]thiadiazol-3-yl-phenylamino)-benzamide; 2-[4-(4-chloro-[1,2,5]thiadiazol-3-yl)-2-methyl-phenylamino]-3,4,5-trifluoro-benzoic acid; 2-[4-(4-chloro-[1,2,5]thiadiazol-3-yl)-2-methyl-phenylamino]-N-cyclopropylmethoxy-3,4,5-trifluoro-benzoic acid; (g) 2-{4-[4-(2-dimethylamino-ethoxy)-[1,2,5]thiadiazol-3-yl]-2-methyl-phenylamino}-3,4,5-trifluoro-benzoic acid; (h) N-cyclopropylmethoxy-3,4,5-trifluoro-2-{2-methyl-4-[4-(2-piperidin-1-yl-ethoxy)-[1,2,5]thiadiazol-3-yl]-phenylamino}-benzamide.

Further preferred compounds include: (a) 5-bromo-2-(2-chloro-4-methylsulfanyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-chloro-4-methanesulfinyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-chloro-4-methanesulfonyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 2-(2-chloro-4-methylsulfanyl-phenylamino)-3,4-difluoro-benzoic acid; 5-bromo-2-(2-chloro-4-methanesulfonyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-Chloro-4-methanesulfonyl-phenylamino)-3,4-difluoro-benzoic acid; (b) 5-bromo-2-(2-

chloro-4-methylsulfanyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methanesulfinyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methanesulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-methylsulfanyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

5 2-(2-chloro-4-methanesulfinyl-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 5-bromo-2-(2-chloro-4-methanesulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methylsulfanyl-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-methanesulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

10 and (c) 2-[2-chloro 4-(3H-imidazol-1-yl)-phenylamino]-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-[1,2,5]thiadiazol-3-yl-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-[4-(2-chloro-4-chloro-[1,2,5]thiadiazol-3-yl)-phenylamino]-3,4,5-trifluoro-benzoic acid; 2-[2-chloro-4-(4-chloro-[1,2,5]thiadiazol-3-yl)-phenylamino]-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-{4-[4-(2-dimethylamino-ethoxy)-[1,2,5]thiadiazol-3-yl]-2-methyl-phenylamino}-3,4,5-trifluoro-benzoic acid; 2-{2-chloro-4-[4-(2-piperidin-1-yl-ethoxy)-[1,2,5]thiadiazol-3-yl]-phenylamino}-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

15 20 Additional preferred compounds include: (a) 2-(2-Chloro-4-ethynyl-phenylamino)-4-fluoro-benzoic acid; 5-Bromo-2-(2-chloro-4-ethynyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-N-hydroxy-3,4,5-trifluoro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(4-Ethynyl-2-chloro-phenylamino)-4-nitro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)-N-Cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-methanesulfinyl-phenylamino)-4-fluoro-N-hydroxy-benzamide; 5-Bromo-2-(4-ethynyl-2-chloro-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; (b) 2-(2-Chloro-4-ethynyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide; 5-Bromo-2-(2-chloro-4-ethynyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-

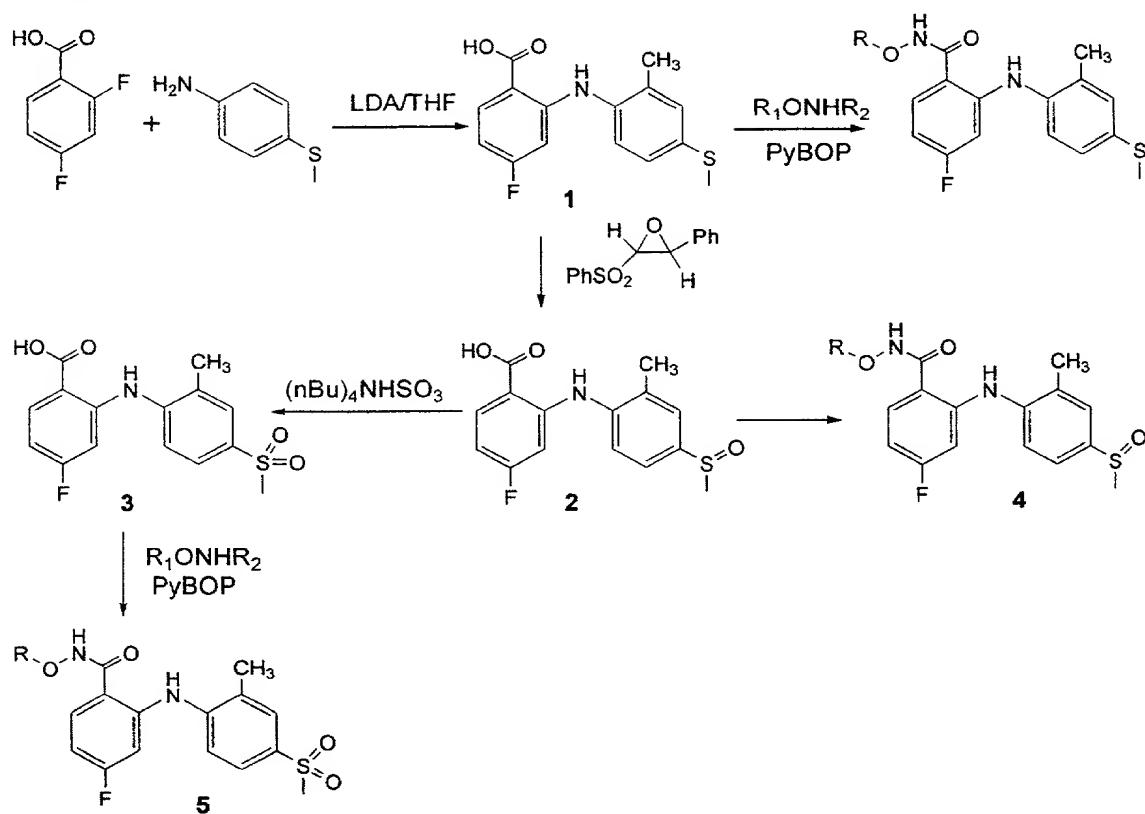
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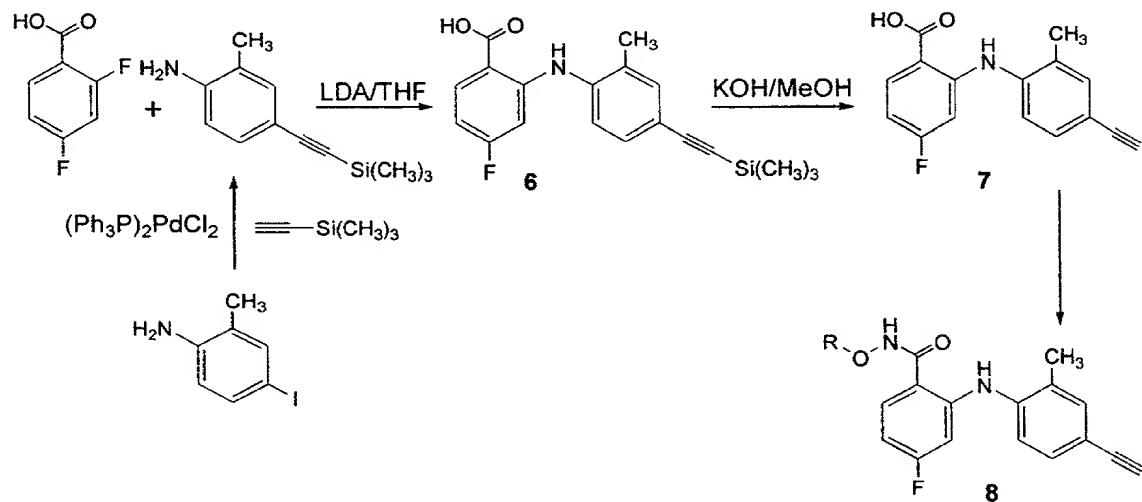
benzamide; 2-(4-Ethynyl-2-chloro-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; 2-(4-Ethynyl-2-chloro-phenylamino)-N-hydroxy-4-nitro-benzamide; and (c) 2-(2-Chloro-4-ethynyl-phenylamino)-4-fluoro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-4-fluoro-benzamide; 2-(2-Chloro-4-methanesulfinyl-phenylamino)- 4-fluoro-N-hydroxy-benzamide; 2-(2-chloro-4-imidazol-1-yl-phenylamino)- 3,4-Difluoro-benzoic acid.

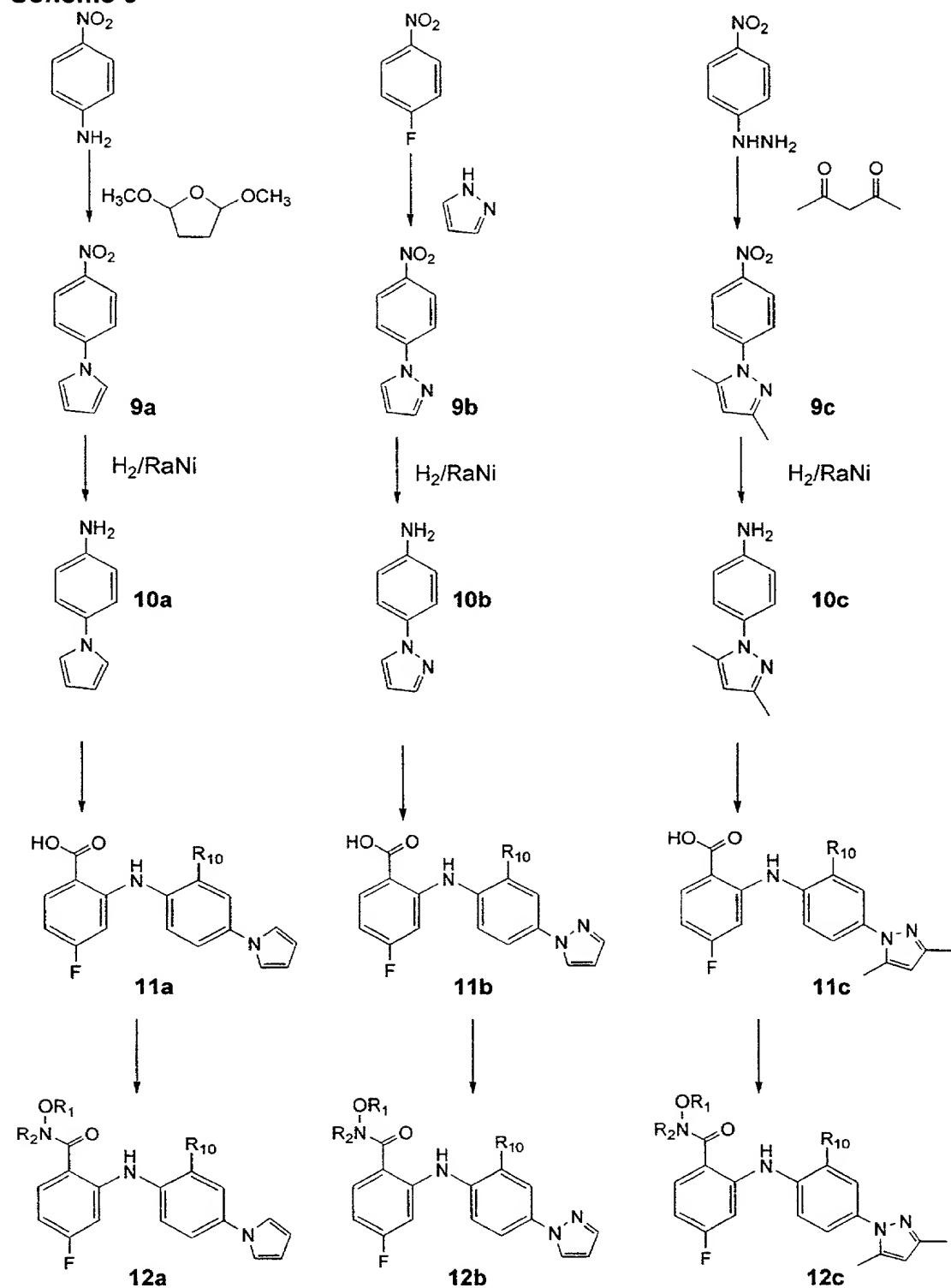
### C. Synthesis

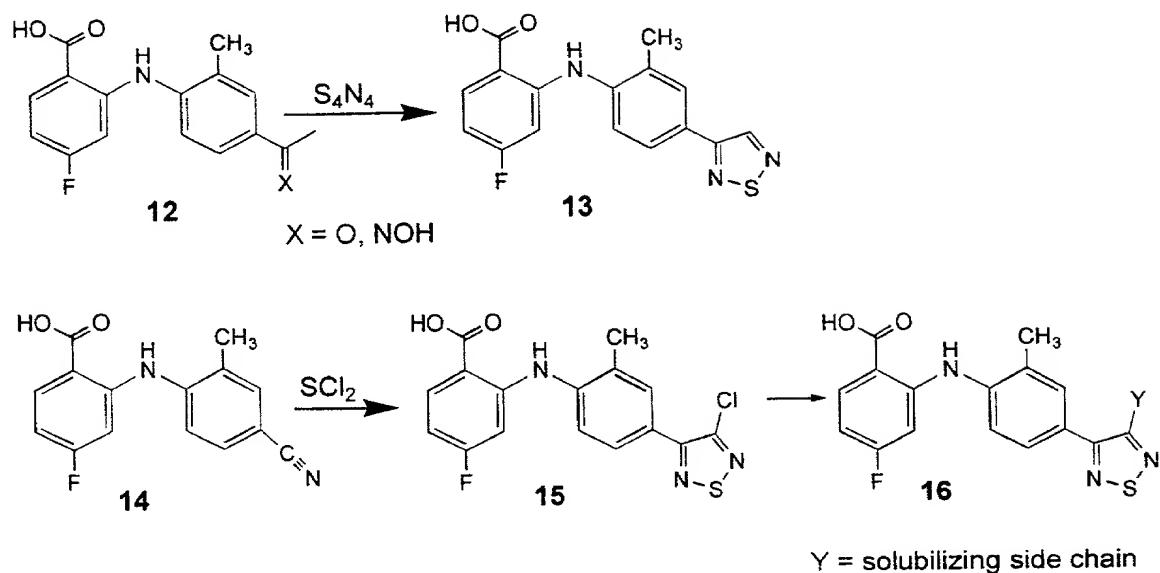
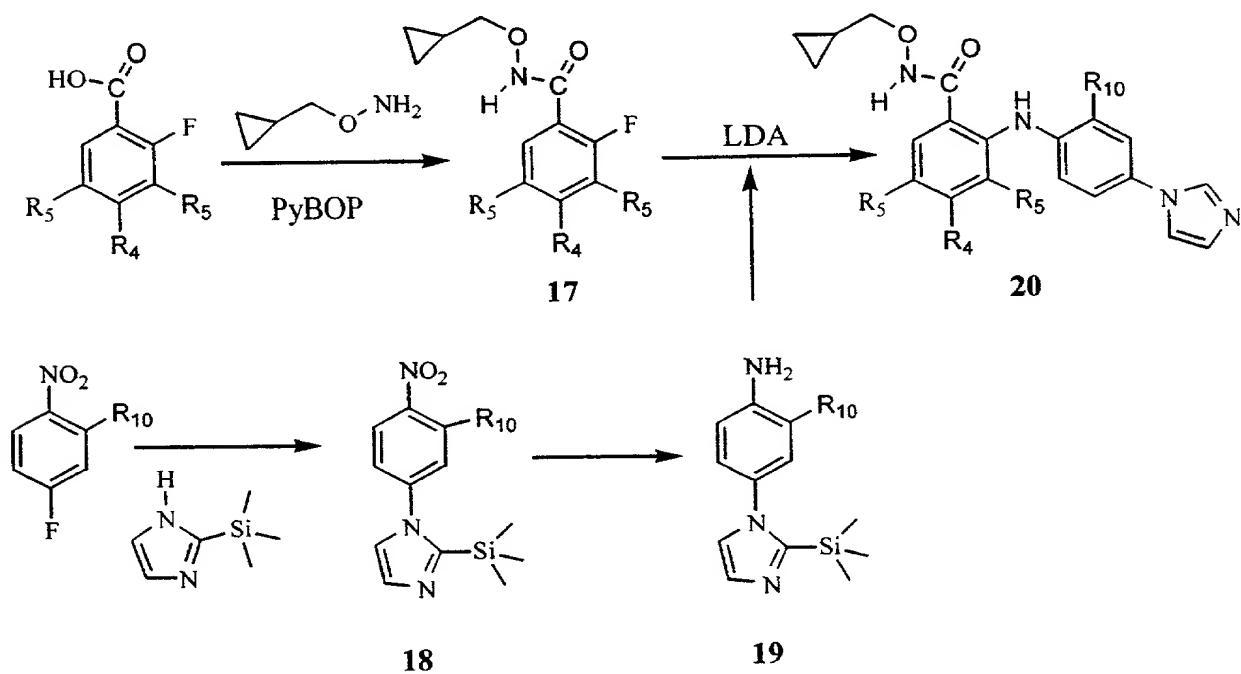
The disclosed compounds can be synthesized according to the following five schemes, or variants thereof. The abbreviation PyBOP is (benzotriazolyl-oxy)-tritypyrrolidino phosphonium hexafluorophosphate. These synthetic strategies are further exemplified in Examples 1-12 below:

**Scheme 1****Scheme 2**

5



**Scheme 3**

**Scheme 4** 3-Aryl-1,2,5-thiadiazols $Y$  = solubilizing side chain**Scheme 5**

#### D. Uses

The disclosed compositions are useful as both prophylactic and therapeutic treatments for diseases or conditions as provided in the Summary section, as well as diseases or conditions modulated by the MEK cascade. Examples include stroke, heart failure, osteoarthritis, rheumatoid arthritis, organ transplant rejection, and a variety of tumors such as ovarian, non-small cell lung, pancreatic, brain, prostatic, renal, and colon.

#### MEK INHIBITION

COMPOUND	IC <sub>50</sub>
4-Fluoro-2-(4-methanesulfanyl-phenylamino)-benzoic acid (1)	1.93 $\mu$ M
4-Fluoro-2-(4-methanesulfinyl-phenylamino)-benzoic acid (2)	> 1 $\mu$ M
4-Fluoro-2-(4-methanesulfonyl-phenylamino)-benzoic acid (3)	316 nM
4-Fluoro-2-(2-methyl-4-trimethylsilyl-ethynyl-phenylamino)-benzoic acid (6)	> 10 $\mu$ M
4-Fluoro-2-(2-methyl-4-ethynyl-phenylamino)-benzoic acid (7)	272 nM

10

#### 1. Dosages

Those skilled in the art will be able to determine, according to known methods, the appropriate dosage for a patient, taking into account factors such as age, weight, general health, the type of symptoms requiring treatment, and the presence of other medications. In general, an effective amount will be between 0.1 and 1000 mg/kg per day, preferably between 1 and 300 mg/kg body weight, and daily dosages will be between 10 and 5000 mg for an adult subject of normal weight. Capsules, tablets or other formulations (such as liquids and film-coated tablets) may be of between 5 and 200 mg, such as 10, 15, 25, 35, 50 mg, 60 mg, and 100 mg and can be administered according to the disclosed methods.

## 2. Formulations

Dosage unit forms include tablets, capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers adapted for subdivision into individual doses.

5 Dosage unit forms can also be adapted for various methods of administration, including controlled release formulations, such as subcutaneous implants. Administration methods include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, local (drops, powders, ointments, gels, or cream), and by inhalation  
10 (a buccal or nasal spray).

Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic

15 esters such as ethyl oleate. Fluidity can be maintained by the use of a coating such as lecithin, a surfactant, or maintaining appropriate particle size. Carriers for solid dosage forms include (a) fillers or extenders, (b) binders, (c) humectants, (d) disintegrating agents, (e) solution retarders, (f) absorption accelerators, (g) adsorbants, (h) lubricants, (i) buffering agents, and  
20 (j) propellants.

Compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents; antimicrobial agents such as parabens, chlorobutanol, phenol, and sorbic acid; isotonic agents such as a sugar or sodium chloride; absorption-prolonging agents such as aluminum monostearate and  
25 gelatin; and absorption-enhancing agents.

## 3. Related compounds

The invention provides the disclosed compounds and closely related, pharmaceutically acceptable forms of the disclosed compounds, such as salts, esters, amides, hydrates or solvated forms thereof; masked or protected forms; 30 and racemic mixtures, or enantiomerically or optically pure forms.

Pharmaceutically acceptable salts, esters, and amides include carboxylate salts (e.g., C<sub>1-8</sub> alkyl, cycloalkyl, aryl, heteroaryl, or non-aromatic heterocyclic),

amino acid addition salts, esters, and amides which are within a reasonable benefit/risk ratio, pharmacologically effective, and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, 5 nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulfonate. These may include alkali metal and alkali earth cations such as sodium, potassium, calcium, and magnesium, as well as non-toxic ammonium, 10 quaternary ammonium, and amine cations such as tetramethyl ammonium, methylamine, trimethylamine, and ethylamine. See, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977, 66:1-19 which is incorporated herein by reference. Representative pharmaceutically acceptable amides of the invention include those derived from ammonia, primary C<sub>1-6</sub> alkyl amines and 15 secondary di (C<sub>1-6</sub> alkyl) amines. Secondary amines include 5- or 6-membered heterocyclic or heteroaromatic ring moieties containing at least one nitrogen atom and optionally between 1 and 2 additional heteroatoms. Preferred amides are derived from ammonia, C<sub>1-3</sub> alkyl primary amines, and di (C<sub>1-2</sub> alkyl)amines. Representative pharmaceutically acceptable esters of the invention include C<sub>1-7</sub> 20 alkyl, C<sub>5-7</sub> cycloalkyl, phenyl, and phenyl(C<sub>1-6</sub>)alkyl esters. Preferred esters include methyl esters.

The invention also includes disclosed compounds having one or more functional groups (e.g., hydroxyl, amino, or carboxyl) masked by a protecting group. Some of these masked or protected compounds are pharmaceutically 25 acceptable; others will be useful as intermediates. Synthetic intermediates and processes disclosed herein, and minor modifications thereof, are also within the scope of the invention.

#### HYDROXYL PROTECTING GROUPS

30 Hydroxyl protecting groups include: ethers, esters, and protection for 1,2- and 1,3-diols. The ether protecting groups include: methyl, substituted methyl

ethers, substituted ethyl ethers, substituted benzyl ethers, silyl ethers and conversion of silyl ethers to other functional groups.

#### Substituted Methyl Ethers

Substituted methyl ethers include: methoxymethyl, methylthiomethyl,

5 *t*-butylthiomethyl, (phenyldimethylsilyl) methoxymethyl, benzyloxymethyl, *p*-ethoxybenzyloxymethyl, (4-methoxyphenoxy) methyl, guaiacolmethyl, *t*-butoxymethyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloro- ethoxy)methyl, 2-(trimethylsilyl)-ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydro-pyranyl, 10 tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl *S,S*-dioxido, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-ethanobenzofuran-2-yl.

15 

#### Substituted Ethyl Ethers

Substituted ethyl ethers include: 1-ethoxyethyl, 1-(2,chloroethoxy)ethyl,

1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, and benzyl.

20 

#### Substituted Benzyl Ethers

Substituted benzyl ethers include: *p*-methoxybenzyl, 3,4-dimethoxybenzyl,

*o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2- and 4-picoly, 3-methyl-2-picoly *N*-oxido, diphenylmethyl, *p*, *p*'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl,  $\alpha$ -naphthyl-

25 diphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)-phenylmethyl, tri-(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyl-diphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-tris(levulinoyloxyphenyl) methyl, 4,4',4"tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)-methyl, 1,1-bis(4-methoxyphenyl)-1'-30 pyrenylmethyl, 9-anthryl, 9-(9-phenyl) xanthenyl, 9-(9-phenyl-10-oxo) anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl *S,S*-dioxido.

### Silyl Ethers

Silyl ethers include: trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethysilyl, 5 and *t*-butylmethoxyphenylsilyl.

### ESTERS

Esters protecting groups include: esters, carbonates, assisted cleavage, miscellaneous esters, and sulfonates.

10 Esters

Examples of protective esters include: formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-*P*-phenylacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-15 (ethylenedithio) pentanoate, pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, and 2,4,6-trimethylbenzoate (mesitoate).

### Carbonates

Carbonates include: methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 20 2-(trimethylsilyl) ethyl, 2-(phenylsulfonyl) ethyl, 2-(triphenylphosphonio) ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, and methyl dithiocarbonate.

### Assisted Cleavage

25 Examples of assisted cleavage protecting groups include: 2-iodobenzoate, 4-azido-butyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl) benzoate, 2-formylbenzene-sulfonate, 2-(methylthiomethoxy) ethyl carbonate, 4-(methylthiomethoxymethyl) benzoate, and 2-(methylthiomethoxymethyl) benzoate.

30 Miscellaneous Esters

In addition to the above classes, miscellaneous esters include: 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl) phenoxyacetate,

2,4-bis(1,1-dimethylpropyl) phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinate, (*E*)-2-methyl-2-butenoate (tiglate), *o*-(methoxycarbonyl) benzoate, *p*-P-benzoate,  $\alpha$ -naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamide, *N*-phenylcarbamate, borate, 5 dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate.

#### Sulfonates

Protective sulfates includes: sulfate, methanesulfonate(mesylate), benzylsulfonate, and tosylate.

### **10 PROTECTION FOR 1,2- AND 1,3-DIOLS**

The protection for 1,2 and 1,3-diols group includes: cyclic acetals and ketals, cyclic ortho esters, and silyl derivatives.

#### Cyclic Acetals and Ketals

Cyclic acetals and ketals include: methylene, ethylidene, 1-*t*-butylethylidene,

15 1-phenylethylidene, (4-methoxyphenyl) ethylidene, 2,2,2-trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, *p*-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, and 2-nitrobenzylidene.

#### Cyclic Ortho Esters

20 Cyclic ortho esters include: methoxymethylene, ethoxymethylene, dimethoxy-methylene, 1-methoxyethylidene, 1-ethoxyethylidene, 1,2-dimethoxyethylidene,  $\alpha$ -methoxybenzylidene, 1-(*N,N*-dimethylamino)ethylidene derivative,  $\alpha$ -(*N,N*-dimethylamino) benzylidene derivative, and 2-oxacyclopentylidene.

### **25 PROTECTION FOR THE CARBOXYL GROUP**

#### ESTERS

Ester protecting groups include: esters, substituted methyl esters, 2-substituted ethyl esters, substituted benzyl esters, silyl esters, activated esters, miscellaneous derivatives, and stanny esters.

### Substituted Methyl Esters

Substituted methyl esters include: 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuryl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxy-methyl, benzyloxymethyl, phenacyl, *p*-bromophenacyl,  $\alpha$ -methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-phthalimidomethyl.

5      methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-phthalimidomethyl.

### 2-Substituted Ethyl Esters

2-Substituted ethyl esters include: 2,2,2-trichloroethyl, 2-haloethyl, *l*-chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2(*p*-nitrophenylsulfonyl)-ethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(2'-pyridyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, *t*-butyl, cyclopentyl, cyclohexyl, allyl, 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl,  $\alpha$ -methylcinnamyl, phenyl, *p*-(methylmercapto)-phenyl, and benzyl.

10     methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-phthalimidomethyl.

### Substituted Benzyl Esters

15     Substituted benzyl esters include: triphenylmethyl, diphenylmethyl, bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-dibenzo-suberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-trimethylbenzyl, *p*-bromobenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfonylbenzyl, piperonyl, and 4-*P*-benzyl.

20     methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-phthalimidomethyl.

### Silyl Esters

Silyl esters include: trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl, and di- *t*-butyldimethylsilyl.

### Miscellaneous Derivatives

25     Miscellaneous derivatives includes: oxazoles, 2-alkyl-1,3-oxazolines, 4-alkyl-5-oxo-1,3-oxazolidines, 5-alkyl-4-oxo-1,3-dioxolanes, ortho esters, phenyl group, and pentaaminocobalt(III) complex.

### Stannyli Esters

Examples of stannyli esters include: triethylstannyli and tri-*n*-butylstannyli.

### AMIDES AND HYDRAZIDES

Amides include: *N,N*-dimethyl, pyrrolidinyl, piperidinyl, 5,6-dihydrophen-anthridinyl, *o*-nitroanilides, *N*-7-nitroindolyl, *N*-8-nitro-1,2,3,4-tetrahydroquinolyl, and *p*-*P*-benzenesulfonamides. Hydrazides include: *N*-phenyl, *N,N*'-diisopropyl

5 and other dialkyl hydrazides.

### PROTECTION FOR THE AMINO GROUP

#### CARBAMATES

10 Carbamates include: carbamates, substituted ethyl, assisted cleavage, photolytic cleavage, urea-type derivatives, and miscellaneous carbamates.

##### Carbamates

Carbamates include: methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydro-thioxanthyl)]methyl, and 4-methoxyphenacyl.

##### Substituted Ethyl

Substituted ethyl protective groups include: 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'-and 4'-pyridyl)ethyl, 2-(*N,N*-icyclohexylcarboxamido)-ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, connamyl, 4-nitrocinnamyl, quinolyl, *N*-hydroxypiperidinyl, alkylthio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, and diphenylmethyl.

##### Assisted Cleavage

Protection via assisted cleavage includes: 2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethyl-thiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolyl-methyl, and 2-(trifluoromethyl)-6-chromonylmethyl.

### Photolytic Cleavage

Photolytic cleavage methods use groups such as: *m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-nitrophenyl)methyl.

### 5 Urea-Type Derivatives

Examples of urea-type derivatives include: phenothiazinyl-(10)-carbonyl derivative, *N*'-*p*-toluenesulfonylaminocarbonyl, and *N*'-phenylaminothiocarbonyl.

### Miscellaneous Carbamates

10 In addition to the above, miscellaneous carbamates include: *t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxy-benzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethyl-carboxamido)-benzyl, 1,1-dimethyl-3(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethyl-propynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-iodoethyl, isobornyl, isobutyl, isonicotinyl, *p*(*p*'-methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1(*p*-henylazophenyl)-ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-trimethylammonium)-benzyl, and 2,4,6-trimethylbenzyl.

### AMIDES

#### Amides

Amides includes: *N*-formyl, *N*-acetyl, *N*-chloroacetyl, *N*-trichloroacetyl, 25 *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridyl-carboxamide, *N*-benzoylphenylalanyl derivative, *N*-benzoyl, and *N*-*p*-phenylbenzoyl.

### Assisted Cleavage

30 Assisted cleavage groups include: *N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N*'-dithiobenzoyloxycarbonylamino)acetyl, *N*-3-

(*p*-hydroxphenyl) propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine derivative, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-oxazolin-2-one.

Cyclic Imide Derivatives

Cyclic imide derivatives include: *N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenyl-maleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl.

SPECIAL -NH PROTECTIVE GROUPS

15 Protective groups for – NH include: *N*-alkyl and *N*-aryl amines, imine derivatives, enamine derivatives, and *N*-hetero atom derivatives (such as *N*-metal, *N*-N, *N*-P, *N*-Si, and *N*-S), *N*-sulphenyl, and *N*-sulfonyl.

*N*-Alkyl and *N*-Aryl Amines

15 *N*-alkyl and *N*-aryl amines include: *N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]-methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, and *N*-2-picolyamine

25 *N*'-oxide.

Imine Derivatives

15 Imine derivatives include: *N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*-(*N*',*N*'-dimethylaminomethylene), *N*,*N*'-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, and *N*-cyclohexylidene.

Enamine Derivative

An example of an enamine derivative is *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl).

N-Hetero Atom Derivatives

*N*-metal derivatives include: *N*-borane derivatives, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, and *N*-copper or *N*-zinc chelate. Examples of *N*-*N* derivatives include: *N*-nitro, *N*-nitroso, and *N*-oxide. Examples of *N*-P derivatives include: *N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, and *N*-diphenyl phosphoryl.

10 Examples of *N*-sulfonyl derivatives include: *N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxy-benzenesulfenyl, *N*-trifluoromethylsulfenyl, and *N*-3-nitropyridinesulfenyl.

15 *N*-sulfonyl derivatives include: *N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl- 4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxy-benzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6-tetramethyl-4-methoxybenzene- sulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy- 4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-*β*-trimethylsilylethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)-benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, and *N*-phenacylsulfonyl.

25 Disclosed compounds which are masked or protected may be prodrugs, compounds metabolized or otherwise transformed *in vivo* to yield a disclosed compound, e.g., transiently during metabolism. This transformation may be a hydrolysis or oxidation which results from contact with a bodily fluid such as blood, or the action of acids, or liver, gastrointestinal, or other enzymes.

Features of the invention are further described in the examples below.

## E. EXAMPLES

## EXAMPLE 1

4-Fluoro-2-(4-methanesulfanyl-phenylamino)-benzoic acid (1).

5 To a solution of 4-(methylmercapto)aniline (3.1622 g, 0.02 mole) in THF at -78°C, a solution of LDA in THF (2M, 30 ml, 0.06 mole) was added and the reaction mixture stirred for 30 minutes at -78°C (Scheme 1). Solid 2,4-difluoro benzoic acid (3.1622 g, 0.02 mole) was added and the reaction stirred for 16 hours while it warmed up to room temperature. The reaction mixture was pour in 10 to ether saturated with HCl gas. HCl gas was bubbled into until precipitation of salts ceased. The precipitated salts were separated by filtration and discarded. The ether layer was concentrated to give **1** as a white solid. Yield 5.63 g (100%); mp 173-179 °C (DEC); <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) <sup>TM</sup> 9.39 (s, 1H), 8.04 (dd, 1H, J=9.2, 6.8 Hz), 7.32-7.17 (AB quartet, 4H), 6.74 (dd, 1H, J=12.1, 2.4 Hz), 6.46-15 6.41 (m, 1H), 2.51 (s, 3H); <sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>) <sup>TM</sup> 172.79, 167.57 (d, J<sub>C-F</sub>=253.4 Hz), 151.55 (d, J<sub>C-F</sub>=12.2 Hz), 136.83, 135.40 (d, J<sub>C-F</sub>=12.2 Hz), 134.72, 128.31, 124.60, 106.51, 105.12 (d, J<sub>C-F</sub>=22.9 Hz), 99.79 (d, J<sub>C-F</sub>=26.7 Hz), 16.51; <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) <sup>TM</sup> -101.39 to -101.46 (m); MS (APCI+) 278 (M+1, 100); IR (KBr) 3319, 1664, 1589, 1258 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>14</sub>H<sub>12</sub>FNO<sub>2</sub>S 20 C, 60.64/60.99; H, 4.36/4.63; N, 5.05/4.80; S, 11.56/10.97.

## EXAMPLE 2

4-Fluoro-2-(4-methanesulfinyl-phenylamino)-benzoic acid (2).

25 A mixture of **1** (Scheme 1) (0.286 g, 0.001031 mole) and oxaziridine (0.235 g, 0.0009 mole) in CHCl<sub>3</sub> (30 ml) at room temperature for 2 hours. The solvent was removed and the resulting brown oil chromatographed on silica column. Elution with CH<sub>2</sub>Cl<sub>2</sub> removed fast moving byproduct. Further elution with CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH (9.5:05), R<sub>f</sub> = 0.27, gave pure **2** as a light brown solid. Yield 132.8 mg (50%); mp 191-192 °C; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>)  $\delta$  9.77 (s, 1H), 8.08 (dd, 1H, J=8.9, 6.7 Hz), 7.70-7.39 (AB quartet, 4H), 6.98 (dd, 1H, J=11.6, 2.4 Hz), 6.57-6.52 (m, 1H), 2.80 (s, 3H); <sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>) <sup>TM</sup> 170.76, 167.18 (d, J<sub>C-F</sub>=253.3 Hz), 149.33 (d, J<sub>C-F</sub>=12.2 Hz), 143.02, 139.50, 135.37 (d, J<sub>C-F</sub>=12.2

Hz), 125.47, 122.32, 108.22, 106.35 (d,  $J_{C-F}=22.8$  Hz), 100.69, (d,  $J_{C-F}=25.9$  Hz), 43.75; MS (APCI+) 294 (M+1, 100); IR (KBr) 1673, 1592, 1228  $\text{cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{14}\text{H}_{12}\text{FNO}_3\text{S}$  C, 57.33/57.48; H, 4.12/4.27; N, 4.78/4.67.

5

## EXAMPLE 3

4-Fluoro-2-(4-methanesulfonyl-phenylamino)-benzoic acid (3).

A solution of **1**(Scheme 1) (0.4458 g, 0.00152 mole) and tetrabutyl-  
ammonium oxon (1.1 g, 0.0030 mole) in  $\text{CH}_2\text{Cl}_2$  (20 ml) was stirred at room  
temperature for 16 hours. TLC showed the presence of starting material; so  
10 additional 1.1 g (0.0030 mole) of the tetrabutylammonium oxon was added and  
reaction mixture stirred for 16 more hours. The reaction mixture was loaded on to  
a silica column and eluted with  $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$  (9.75:0.25) and the fast moving  
fraction collected and concentrated to give **3** as a white solid. Yield, 0.3856 g  
(82%); mp 200-202  $^{\circ}\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ )  $\delta$  9.78 (s, 1H), 8.13 (dd, 1H,  
15  $J=8.9, 6.5$  Hz), 7.94-7.38 (AB quartet, 4H), 7.10 (dd, 1H,  $J=11.3, 2.4$  Hz), 6.66-  
6.61 (m, 1H), 3.09 (s, 3H);  $^{13}\text{C-NMR}$  (100 MHz;  $\text{CDCl}_3$ )  $\delta$  171.52, 167.28 (d,  
 $J_{C-F}=254.9$  Hz), 148.32, 145.21, 135.59 (d,  $J_{C-F}=11.5$  Hz), 134.50, 129.39,  
120.62, 108.74, 107.46 (d,  $J_{C-F}=22.8$  Hz), 101.61 (d,  $J_{C-F}=26.7$  Hz), 44.78;  $^{19}\text{F-NMR}$   
(376 MHz;  $\text{CDCl}_3$ )  $\delta$  -100.29 to -100.45 (m); MS (APCI+) 310 (M+1, 100);  
20 (APCI-) 308 (M-1, 100); Anal. calcd/found for:  $\text{C}_{14}\text{H}_{12}\text{FNO}_4\text{S}\cdot 0.75\text{ H}_2\text{O}$  C,  
52.08/52.36; H, 4.22/3.88; N, 4.34/4.26.

## EXAMPLE 4

2-methyl-4-trimethylsilyl-ethynyl-aniline (5)

25 To a solution of 4-iodo-2-methyl-aniline (2.33g, 10 mmol),  
bis(triphenylphosphine)palladium(II)chloride (1.4g, 0.2 mmol), CuI (0.19 g, 0.1  
mmol) in  $\text{Et}_3\text{N}$  (40 ml) at ice-bath temperature, (trimethylsilyl)acetylene (1.18 g,  
12 mmol) was added dropwise (Scheme 2). After an hour stirring, the ice-bath  
was removed and the reaction mixture heated at 40 $^{\circ}\text{C}$  (oil-bath temperature) for  
30 one hour; cooled to room temperature and the solvent removed. The residue  
was partitioned between  $\text{H}_2\text{O}$  and  $\text{Et}_2\text{O}$ . The  $\text{Et}_2\text{O}$  layer was separated, dried  
( $\text{MgSO}_4$ ) and concentrated to give an oil. The oil was purified by silica column,

eluting with  $\text{CH}_2\text{Cl}_2$ . The fraction with  $R_f = 0.37$  was collected and concentrated to give 2-methyl-4-trimethylsilanyl-ethynyl-aniline as a dark brown oil. Yield 1.50 g (83%).

5

## EXAMPLE 5

4-Fluoro-2-(2-methyl-4-trimethylsilanyl-ethynyl-phenylamino)-benzoic acid (6)

Continuing after Example 4, to a solution of 2-methyl-4-trimethylsilanyl-ethynyl aniline (1.50 g, 0.008 mole) in THF (10 ml) at  $-78^\circ\text{C}$ , LDA (2 M in THF, 6 ml, 0.012 mole) was added and the mixture was stirred at  $-78^\circ\text{C}$  for 30 minutes. Solid 2,4-difluoro-benzoic acid (0.633 g, 0.004 mole) was added and the stirred for 16 hours while it warmed up to room temperature. The solvents were removed and water (30 ml) and  $\text{Et}_2\text{O}$  (50 ml) added to the oil residue. The mixture was stirred vigorously and the  $\text{Et}_2\text{O}$  layer separated, dried ( $\text{MgSO}_4$ ) and concentrated to give a brown solid. The solid was purified on silica column, eluted with  $\text{CH}_2\text{Cl}_2$ . The fraction with  $R_f = 0.37$  was collected and concentrated to give a light brown solid. The solid was added to pentane; some insoluble brown particulate was separated by filtration and discarded. The pentane layer was concentrated to give **6** as a light yellow solid. Yield 0.65 g (47%); mp 170-171°C;  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ )  $\delta$  9.33 (s, 1H), 8.05 (dd, 1H,  $J=8.9, 6.8$  Hz), 7.43 (d, 1H,  $J=1.2$  Hz), 7.35 (dd, 1H,  $J=8.2, 1.7$  Hz), 7.25 (d, 1H,  $J=8.2$  Hz), 6.53 (dd, 1H,  $J=11.8, 2.4$  Hz), 6.47-6.42 (m, 1H), 2.25 (s, 3H), 0.26 (s, 9H);  $^{13}\text{C-NMR}$  (100 MHz;  $\text{CDCl}_3$ )  $\square$  172.86, 167.61 (d,  $J_{\text{C-F}}=253.3$ ), 151.24 (d,  $J_{\text{C-F}}=12.3$  Hz), 138.28, 135.38 (d,  $J_{\text{C-F}}=11.4$  Hz), 134.85, 132.82, 130.63, 123.81, 119.91, 106.63, 105.23 (d,  $J_{\text{C-F}}=22.8$  Hz), 104.77, 99.98 (d,  $J_{\text{C-F}}=26.7$  Hz), 94.05, 17.78, 0.00; MS (APCI+) 342 (M+1, 100); IR (KBr) 2151, 1661, 1249  $\text{cm}^{-1}$ ; Anal. calcd/ found for:  $\text{C}_{19}\text{H}_{20}\text{FNO}_2\text{Si}$  C, 66.83/67.02; H, 5.90/6.00; N, 4.10/4.09; F, 5.56/5.45.

## EXAMPLE 6

4-Fluoro-2-(2-methyl-4-ethynyl-phenylamino)-benzoic acid (7).

To a solution of **6** in  $\text{CH}_3\text{OH}$  (30 ml), aqueous 1N KOH (10 ml) was added. After stirring at room temperature for 16 hours, the  $\text{CH}_3\text{OH}$  was removed and the

aqueous layer was acidified with 6N HCl (Scheme 2). The resulting white precipitation was extracted in to Et<sub>2</sub>O, the Et<sub>2</sub>O layer was dried (MgSO<sub>4</sub>) and concentrated to give 7 as tan colored solid. Yield 0.4274 g (91%); mp 177-178 °C; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 9.35 (s, 1H), 8.08-8.04 (m, 1H), 7.44 (s, 1H),

5 7.38-7.25 (m, 2H), 6.57 (d, 1H, J=11.8 Hz), 6.48-6.44 (m, 1H), 3.08 (s, 1H), 2.27 (s, 3H); <sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>) <sup>TM</sup> 172.84, 167.61 (d, J<sub>C-F</sub>=253.3), 151.15 (d, J<sub>C-F</sub>=12.3 Hz), 138.63, 135.40 (d, J<sub>C-F</sub>=12.3 Hz), 135.00, 132.87, 130.81, 123.76, 118.79, 106.75, 105.33 (d, J<sub>C-F</sub>=22.8 Hz), 100.03 (d, J<sub>C-F</sub>=26.0 Hz), 83.37, 17.83, 0.00; <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) <sup>TM</sup> -101.24 to -101.31 (m); MS (APCI+) 270 (M+1, 100); IR (KBr) 3315, 1672, 1594, 1253 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>16</sub>H<sub>12</sub>FNO<sub>2</sub> C, 71.37/71.08; H, 4.49/4.82; N, 5.20/5.09.

#### EXAMPLE 7

##### 1-(4-nitro-phenyl)-1H-pyrrole (9a)

15 To a gently refluxing mixture of 4-nitroaniline (6.906 g, 0.05 mole), and sodium acetate (23 g, 0.28 mole) in acetic acid (100 ml) was added 2,5-dimethoxytetrahydrofuran (7.26 g, 7.12 ml, 0.055 mole) dropwise (Scheme 3). After refluxing for 3 hours, the reaction mixture was poured on to crushed ice (~250 ml), basified with 10 % sodium hydroxide (250 ml) and extracted with 20 CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was dried (K<sub>2</sub>CO<sub>3</sub>) to afford the product as a dark brown oil. Yield 9.40 g (100 %).

#### EXAMPLE 8

##### 1-(4-nitro-phenyl)-1H-pyrazole (9b)

25 A mixture of pyrazole (6.808 g, 0.1 mole) tetrabutylammonium bromide (3.22 g, 0.01 mole) and KOH (11.22 g, 0.2 mole) were ground together and sonicated for 16 hours. To this 1-fluoro-4-nitrobenzene (15.521 g, 11.67 ml, 0.11 mole) was added and the mixture sonicated for 24 hours. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was dried (MgSO<sub>4</sub>) and 30 concentrated to give dark brown solid. This was purified by silica column chromatography. Elution with CH<sub>2</sub>Cl<sub>2</sub> (R<sub>f</sub> = 0.44) gave the product as a light

brown solid. Yield 8.80 g (47 %); mp 171-172 °C; Anal. calcd/found for: C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub> C, 57.14/56.52; H, 3.73/3.62; N, 22.21/21.95.

#### EXAMPLE 9

5 3,5-dimethyl-1-(4-nitro-phenyl)-1H-pyrazole (9c)

To a solution of 4-nitro-phenyl-hydrazine (15.3 g, 0.1 mole) and 2,4-pentanedione (10.01 g, 10.27 ml, 0.1 mole) in EtOH (200 ml) were added 5 drops of concentrated HCl. The mixture was refluxed for 15 minutes; and the solvent removed to give a gummy product. This was purified by silica column chromatography. Elution with CH<sub>2</sub>Cl<sub>2</sub> gave the desired product (R<sub>f</sub> = 0.10) as a brown solid. Yield 7.22 g (33 %).

#### EXAMPLE 10

4-Pyrrol-1-yl-phenylamine (10a)

15 Catalytic reduction (H<sub>2</sub>/RaNi (5 g) /THF) of 1-(4-nitro-phenyl)- 1H-pyrrole (9.69 g, 0.05149 mole) at 51 psi gave crude product as an oil (Scheme 3). The product was purified by silica column chromatography. Elution with CH<sub>2</sub>Cl<sub>2</sub> (R<sub>f</sub> = 0.13) gave the pure product as white solid. Yield 8.06 g (99 %); mp 80-81 °C.

20

#### EXAMPLE 11

In a manner similar to the preparation of 4-pyrrol-1-yl-phenylamine, the following were prepared:

25 4-1H-Pyrazol-1-yl-phenylamine (10b). Dark brown oil, yield 6.26 g (100 %).

Benzenamine, 4-(3,5-dimethyl-1H-pyrazol-1-yl) (10c). Dark brown oil.

Yield 6.45 g (100 %).

30

#### EXAMPLE 12

4-Fluoro-2-(4-pyrrol-1-yl-phenylamino)-benzoic acid (11a)

To a solution of 4-pyrrol-1-yl-phenylamine (3.16 g, 0.02 mole) in THF

(30 ml) at -78°C, a solution of LDA (2M, 15 ml, 0.03 mole) was added and the mixture stirred for 30 minutes. Solid 2,4-difluorobenzoic acid was added and the reaction mixture stirred for 16 hours as it warmed up to room temperature. The solvent was removed and ether (100 ml) added to the dark oily residue. This was 5 stirred vigorously and the insoluble gummy precipitate separated by filtration. The gamy residue was dissolved in H<sub>2</sub>O, acidified to pH 1 with 10% HCl, and extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O layer was dried (MgSO<sub>4</sub>) and concentrated to give the target compound as a brown solid. Yield 2.74 g (93 %); mp 223-225 °C (DEC); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -101.44 (s); MS (APCI+) 297 (M+1, 100); IR 10 (KBr) 1658, 1526, 1254 cm<sup>-1</sup>.

In a manner similar to the preparation of 4-Fluoro-2-(4-pyrrol-1-yl-phenylamino)-benzoic acid, the following were prepared:

15 4-Fluoro-2-(4-pyrazol-1-yl-phenylamino)-benzoic acid (11b). Light brown solid, mp 212-213 °C.

2-[4-(3,5-Dimethyl-pyrazol-1-yl)-phenylamino]- 4-Fluoro benzoic acid (11c). Tan powder, mp 198 –200 °C.

20

#### EXAMPLE 13

##### Cascade assay for inhibitors of the MAP kinase pathway

Incorporation of <sup>32</sup>P into myelin basic protein (MBP) is assayed in the presence of a glutathione S-transferase fusion protein containing p44MAP kinase 25 (GST-MAPK) and a glutathione S-transferase fusion protein containing p45MEK (GST-MEK). The assay solution contains 20 mM HEPES, pH 7.4, 10 mM MgCl<sub>2</sub>, 1 mM MnCl<sub>2</sub>, 1 mM EGTA, 50,μM [γ-<sup>32</sup>P]ATP, 10 μg GST-MEK, 0.5 μg GST-MAPK and 40 μg MBP in a final volume of 100 μL. Reactions are stopped after 20 minutes by addition of trichloroacetic acid and filtered through a GF/C 30 filter mat. <sup>32</sup>P retained on the filter mat is determined using a 120S Betaplate. Compounds are assessed at 10 μM for ability to inhibit incorporation of <sup>32</sup>P.

To ascertain whether compounds are inhibiting GST-MEK or GST MAPK, two additional protocols are employed. In the first protocol, compounds are added to tubes containing GST-MEK, followed by addition of GST-MAPK, MBP and [ $\gamma$ -<sup>32</sup>P]ATP. In the second protocol, compounds are added to tubes

5 containing both GST-MEK and GST-MAPK, followed by MBP and [ $\gamma$ -<sup>32</sup>P]ATP.

Compounds that show activity in both protocols are scored as MAPK inhibitors, while compounds showing activity in only the first protocol are scored as MEK inhibitors.

10 EXAMPLE 14

In vitro MAP kinase assay

Inhibitory activity can be confirmed in direct assays. For MAP kinase, 1  $\mu$ g GST-MAPK is incubated with 40  $\mu$ g MBP for 15 minutes at 30°C in a final volume of 50  $\mu$ L containing 50 mM Tris (pH 7.5), 10  $\mu$ M MgCl<sub>2</sub>, 2  $\mu$ M EGTA, and 15 10  $\mu$ M [ $\gamma$ -<sup>32</sup>P]ATP. The reaction is stopped by addition of Laemmli SDS sample buffer and phosphorylated MBP resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into MBP is determined by both autoradiography, and scintillation counting of excised bands.

20 EXAMPLE 15

In vitro MEK assay

For evaluation of direct MEK activity, 10  $\mu$ g GST-MEK<sub>1</sub> is incubated with 5  $\mu$ g of a glutathione S-transferase fusion protein containing p44MAP kinase with a lysine to alanine mutation at position 71 (GST-MAPK-KA). This mutation eliminates kinase activity of MAPK, so only kinase activity attributed to the added MEK remains. Incubations are 15 minutes at 30°C in a final volume of 50  $\mu$ L containing 50 mM Tris (pH 7.5), 10  $\mu$ M MgCl<sub>2</sub>, 2  $\mu$ M EGTA, and 10  $\mu$ M [ $\gamma$ -<sup>32</sup>P]ATP. The reaction is stopped by addition of Laemml SDS sample buffer. Phosphorylated GST-MAPK-KA is resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into GST-MAPK-KA is determined by autoradiography, and subsequent scintillation counting of excised bands.

Additionally, an artificially activated MEK containing serine to glutamate mutations at positions 218 and 222 (GST-MEK-2E) is used. When these two sites are phosphorylated, MEK activity is increased. Phosphorylation of these sites can be mimicked by mutation of the serine residues to glutamate. For this 5 assay, 5 µg GST-MEK-2E is incubated with 5 µg GST-MAPK-KA for 15 minutes at 30°C in the same reaction buffer as described above. Reactions are terminated and analyzed as above.

#### EXAMPLE 16

10 Whole cell MAP kinase assay

To determine if compounds block activation of MAP kinase in whole cells, the following protocol is used. Cells are plated in multi-well plates and grown to confluence. Cells are serum-deprived overnight. Cells are exposed to the desired concentrations of compound or vehicle (DMSO) for 30 minutes, followed 15 by addition of a growth factor, for example, PDGF (100 ng/mL). After a 5-minute treatment with the growth factor, cells are washed with PBS, and lysed in a buffer consisting of 70 mM NaCl, 10 mM HEPES (pH 7.4), 50 mM glycerol phosphate, and 1% Triton X-100. Lysates are clarified by centrifugation at 13,000 x g for 10 minutes. Five to fifteen micrograms of protein from the resulting supernatants 20 are subjected to SDS/PAGE and Western blotting for phosphorylated MAP kinase levels.

#### EXAMPLE 17

Monolayer growth

25 Cells are plated into multi-well plates at 10 to 20,000 cells/mL. Forty-eight hours after seeding, test compounds are added to the cell growth medium and incubation is continued for 2 additional days. Cells are then removed from the wells by incubation with trypsin and enumerated with a Coulter counter.

## EXAMPLE 18

Growth in soft-agar

Cells are seeded into 35-mm dishes at 5 to 10,000 cells/dish using growth medium containing 0.3% agar. After chilling to solidify the agar, cells are 5 transferred to a 37°C incubator. After 7 to 10 days' growth, visible colonies are manually enumerated with the aid of a dissecting microscope.

## EXAMPLE 19

Collagen-Induced Arthritis in Mice

10 Type II collagen-induced arthritis (CIA) in mice is an experimental model of arthritis that has a number of pathologic, immunologic, and genetic features in common with rheumatoid arthritis. The disease is induced by immunization of DBA/1 mice with 100 µg type II collagen, which is a major component of joint cartilage, delivered intradermally in Freund's complete adjuvant. The disease 15 susceptibility is regulated by the class II MHC gene locus, which is analogous to the association of rheumatoid arthritis with HLA-DR4.

A progressive and inflammatory arthritis develops in the majority of mice immunized, characterized by paw width increases of up to 100%. A test compound is administered to mice in a range of amounts, such as 20, 60, 100, 20 and 200 mg/kg body weight/day. The duration of the test can be several weeks to a few months, such as 40, 60, or 80 days. A clinical scoring index is used to 25 assess disease progression from erythema and edema (stage 1), joint distortion (stage 2), to joint ankylosis (stage 3). The disease is variable in that it can affect one or all paws in an animal, resulting in a total possible score of 12 for each mouse. Histopathology of an arthritic joint reveals synovitis, pannus formation, and cartilage and bone erosions. All mouse strains that are susceptible to CIA are high antibody responders to type II collagen, and there is a marked cellular response to CII.

## EXAMPLE 20

SCW-induced monoarticular arthritis

Arthritis is induced as described by Schwab, et al., *Infection and Immunity*, 59:4436-4442 (1991) with minor modifications. Rats receive 6 µg sonicated SCW [in 10 µl Dulbecco's PBS (DPBS)] by an intraarticular injection into the right tibiotalar joint on day 0. On day 21, the DTH is initiated with 100 µg of SCW (250 µl) administered i.v. For oral compound studies, compounds are suspended in vehicle (0.5% hydroxypropyl-methylcellulose/0.2% Tween 80), sonicated, and administered twice daily (10 ml/kg volume) beginning 1 hr prior to reactivation with SCW. Compounds are administered in amounts between 10 and 500 mg/kg body weight/day, such as 20, 30, 60, 100, 200, and 300 mg/kg/day. Edema measurements are obtained by determining the baseline volumes of the sensitized hindpaw before reactivation on day 21, and comparing them with volumes at subsequent time points such as day 22, 23, 24, and 25. Paw volume is determined by mercury plethysmography.

## EXAMPLE 21

Mouse ear-heart transplant model

Fey, T.A. et al. describe methods for transplanting split-heart neonatal cardiac grafts into the ear pinna of mice and rats (*J. Pharm. and Toxic. Meth.* 39:9-17 (1998)). Compounds are dissolved in solutions containing combinations of absolute ethanol, 0.2% hydroxypropyl methylcellulose in water, propylene glycol, cremophor, and dextrose, or other solvent or suspending vehicle. Mice are dosed orally or intraperitoneally once, twice or three times daily from the day of transplant (day 0) through day 13 or until grafts have been rejected. Rats are dosed once, twice, or three times daily from day 0 through day 13. Each animal is anesthetized and an incision is made at the base of the recipient ear, cutting only the dorsal epidermis and dermis. The incision is spread open and down to the cartilage parallel to the head, and sufficiently wide to accommodate the appropriate tunneling for a rat or insertion tool for a mouse. A neonatal mouse or rat pup less than 60 hours old is anesthetized and cervically dislocated. The

heart is removed from the chest, rinsed with saline, bisected longitudinally with a scalpel, and rinsed with sterile saline. The donor heart fragment is placed into the preformed tunnel with the insertion tool and air or residual fluid is gently expressed from the tunnel with light pressure. No suturing, adhesive bonding, 5 bandaging, or treatment with antibiotics is required.

Implants are examined at 10-20-fold magnification with a stereoscopic dissecting microscope without anesthesia. Recipients whose grafts are not visibly beating may be anesthetized and evaluated for the presence of electrical activity using Grass E-2 platinum subdermal pin microelectrodes placed either in 10 the pinna or directly into the graft and a tachograph. Implants can be examined 1-4 times a day for 10, 20, 30 or more days. The ability of a test compound to ameliorate symptoms of transplant rejection can be compared with a control compound such as cyclosporine, tacrolimus, or orally-administered lefluonamide.

15 **EXAMPLE 22**

Murine ovalbumin-induced eosinophilia

Female C57BL/6 mice are obtained from the Jackson Laboratory (Bar Harbor, ME). All animals are given food and water ad libitum. Mice are sensitized 20 with a single i.p. injection of OVA (grade V, Sigma Chemical Company, St. Louis, MO) adsorbed to alum, (10 µg OVA + 9 mg alum in 200 µl saline) or vehicle control, (9 mg alum in 200 µl saline) on day 0. On day 14, the mice are challenged with a 12-minute inhalation of an aerosol consisting of 1.5% OVA 25 (weight/volume) in saline produced by a nebulizer (small particle generator, model SPAG-2; ICN Pharmaceuticals, Costa Mesa, CA). Groups of eight mice are dosed with oral vehicle (0.5% hydroxypropylmethylcellulose / 0.25% TWEEN-80), or a test compound at 10, 30, or 100 mg/kg in oral vehicle, 200 µl per mouse p.o. Dosing is performed once per day starting on day 7 or day 13, and extending through day 16.

30 For determination of pulmonary eosinophilia, three days after the first OVA aerosol challenge (day 17), the mice are anesthetized with an i.p. injection of anesthetic (Ketamine/Acepromazine/Xylazine), and the tracheae is exposed

and cannulated. The lungs and upper airways are lavaged twice with 0.5 ml of cold PBS. A portion (200  $\mu$ l) of the bronchoalveolar lavage (BAL) fluid is enumerated using a Coulter counter Model ZB1 (Coulter Electronics, Hialeah, FL). The remaining BAL fluid is then centrifuged at 300 x g for five minutes, and 5 the cells are resuspended in 1 ml of HBSS (Gibco BRL) containing 0.5% fetal calf serum (HyClone) and 10 mM HEPES (Gibco BRL). The cell suspension is centrifuged in a cytospin (Shandon Southern Instruments, Sewickley, PA) and stained by Diff Quick (American Scientific Products, McGraw Park, IL) to 10 differentiate BAL leukocytes into neutrophil, eosinophil, monocyte or lymphocyte subsets. The number of eosinophils in the BAL fluid is determined by multiplying the percentage of eosinophils by the total cell count.

#### EXAMPLE 23

##### Caco-2 cell studies

15 Cell transport studies were conducted with Caco-2 cells grown on Snapwells between 22 to 28 days postseeding. Typically, 10 mM MES buffer (pH 6.5) with 5 mM KCl, 135 mM NaCl and 1.8 mM CaCl<sub>2</sub> was used for the apical side and 10 mM MOPS (pH 7.4) with 5 mM KCl, 132.5 mM NaCl and 1.8 mM 20 CaCl<sub>2</sub> with 5 mM D-Glucose was used for the basolateral side. After washing the monolayers, appropriate buffers were pipetted into the respective chambers and the cells were pre-equilibrated at 37°C for at least 15 min. On the day of the experiment the growth media was aspirated and the cell monolayers were preequilibrated with appropriate buffers at 37°C for at least 15 min. Thereafter, 25 TEER measurements were performed to confirm the integrity of the monolayers. Transepithelial flux measurements were made by mounting the cell monolayers in a side-by-side diffusion chamber system (Precision Instrument Design, Tahoe City, CA). Temperature was maintained at 37°C with a circulating water jacket. The solutions were mixed with gas-lift circulation with 95% oxygen-5% carbon 30 dioxide. Donor solutions with PD compounds, [<sup>14</sup>C] mannitol (leakage marker) and [<sup>3</sup>H] metoprolol (reference compound) were added to the apical chamber. Donor and receiver samples were collected at selected time intervals for up to 3

hours. Radiolabelled mannitol and metoprolol were analyzed using scintillation counting (TopCount, Packard Instruments, Downers Grove, IL). PD compounds were analyzed using a LC/MS/MS method. Apparent permeability coefficients were calculated using the following equation:

5  $P_{app} = (V^* dC) / (A.C_0. dt)$

where  $V$  = volume of the receiver solution in ml,  $A$  = surface area in  $cm^2$ ,  $C_0$  = initial donor concentration in mM and  $dC/dt$  = change in the drug concentration in the receiver chamber over time.

10 EXAMPLE 24

Metabolic Stability in Human and Rat Liver Microsomes

Compounds are individually incubated (5  $\mu$ M, dissolved in DMSO) with human and rat liver microsomes (0.5 mg/mL protein) in 50 mM KHPO<sub>4</sub> buffer at 15 37°C in the presence of 1.0 mM NADPH. At 0, 10, 20 and 40 minutes, 100  $\mu$ L aliquots are removed and added to 300  $\mu$ L of acetonitrile. Standard curves are run in a similar manner with each compound at concentrations: 7.5  $\mu$ M, 3.75  $\mu$ M, 2.5  $\mu$ M, 1.25  $\mu$ M. The samples are analyzed for parent concentration by LC/MS/MS. The in vitro metabolic half-life determinations are determined from 20 the concentration vs. time plots using WinNonlin. These in vitro data represent the rate of oxidative and hydrolytic metabolism.

EXAMPLE 25

25 Preparation of 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide (PD 297447)

Step a: Preparation of N-Cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide

To a stirring suspension comprised of O-cyclopropylmethyl-hydroxylamine 30 hydrochloride (5.40 g,  $43.7 \times 10^{-3}$  mol) in dichloromethane (20 ml) at ambient temperature under a nitrogen atmosphere was added directly diisopropylethylamine (10.8 ml, 0.062 mol). A solution comprised of 2,3,4-

trifluorobenzenesulfonyl chloride (1.00 g,  $4.34 \times 10^{-3}$  mol) in dichloromethane (120 ml) was added as a slow steady stream over twelve minutes to the first solution. After twelve minutes of stirring the combined reaction mixture, a 10 % aqueous hydrochloric acid solution (140 ml) was added. The biphasic mixture was stirred vigorously and the layers were separated. The organic phase was dried ( $MgSO_4$ ) and concentrated to 6 ml volume. The concentrate was applied to a flash silica column (90 g of silica). Elution with dichloromethane afforded 0.83 g of the white amorphous solid product; 68 % yield;  $^1H$ -NMR (400 MHz;  $CDCl_3$ )  $\delta$  7.50 (m, 1H), 7.10 (s, 1H), 6.95 (m, 1H), 3.59 (d, 2H,  $J=7.2$  Hz), 0.80 (m, 1H), 0.31 (m, 2H), 0.02 (m, 2H);  $^{19}F$ -NMR (376 MHz;  $CDCl_3$ )  $\delta$  -122.65 (m, 1F), -129.37 (m, 1F), -156.20 (m, 1F); MS (APCI-) 280 (M-1, 100), 210 (55), 195 (45).

**Step b: Preparation of 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide**

To a stirring solution comprised of 2-chloro-4-iodoaniline (0.80 g,  $3.2 \times 10^{-3}$  mol) in tetrahydrofuran (10 ml) at  $-78$  °C under a nitrogen atmosphere was added 1.0 molar lithium *bistrimethylsilylamide* solution in tetrahydrofuran (6.2 ml,  $6.2 \times 10^{-3}$  mol) to form a green suspension. The suspension was stirred for five minutes before a stirring suspension comprised of lithiated *N*-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide [prepared by adding 3.0 ml of the 1.0 molar lithium *bistrimethylsilylamide* solution to a stirring solution comprised of 0.83 g ( $2.95 \times 10^{-3}$  mol) of *N*-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide in 10 ml of tetrahydrofuran at  $-78$  °C] was added. The cold bath was removed and the reaction mixture was stirred for one hour. Aqueous (10 %) hydrochloric acid (50 ml) was added to the reaction mixture, and the biphasic mixture was concentrated *in vacuo* to an aqueous suspension that was extracted with diethyl ether (200 ml). The ether phase was dried ( $MgSO_4$ ) and concentrated *in vacuo* to afford 2 g of a tan oil. The crude product was purified by flash silica chromatography. Elution with a gradient [99:1 hexanes-ethyl acetate  $\rightarrow$  (2 min) 9:1  $\rightarrow$  (25 min) 3:1] afforded 1.10 g of a clear amorphous foam; 73 % yield;  $^1H$ -NMR (400 MHz; DMSO)  $\delta$  7.69 (m, 1H), 7.59 (d, 1H,  $J=1.9$

Hz), 7.34 (dd, 1H, J=8.7, 1.9 Hz), 7.27 (s, 1H), 7.00 (s, 1H), 6.95 (m, 1H), 6.43 (dd, 1H, J=8.7, 5.8 Hz), 3.52 (d, 2H, J=7.5 Hz), 0.74 (m, 1H), 0.34 (m, 2H), 0.02 (m, 2H);  $^{19}\text{F}$ -NMR (376 MHz;  $\text{CDCl}_3$ )  $\delta$  -124.76 (m, 1F), -136.69 (d, 1F, J=18.3 Hz); MS (APCI+) 515 (M+1, 100); (APCI-) 513 (M-1, 50), 443 (73), 428 (100); IR (KBr) 1491  $\text{cm}^{-1}$ ; Anal. Calcd/found for  $\text{C}_{16}\text{H}_{14}\text{ClF}_2\text{IN}_2\text{O}_3\text{S}$  C, 37.34/36.54; H, 2.74/2.71; N, 5.44/5.15; F, 7.38/7.57.

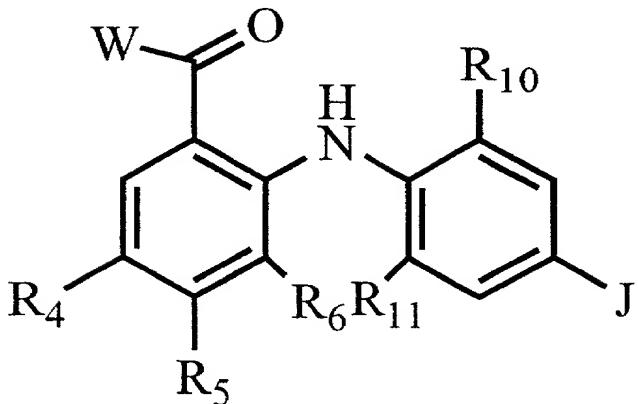
## F. OTHER EMBODIMENTS

From the above disclosure and examples, and from the claims below, the essential features of the invention are readily apparent. The scope of the invention also encompasses various modifications and adaptations within the knowledge of a person of ordinary skill. Examples include a disclosed compound modified by addition or removal of a protecting group, or an ester, pharmaceutical salt, hydrate, acid, or amide of a disclosed compound. Publications cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

CLAIMS

1. A compound of formula (I):



(I)

10

wherein

W is OR<sub>1</sub>, NR<sub>2</sub>OR<sub>1</sub>, NR<sub>A</sub>R<sub>B</sub>, NR<sub>2</sub>NR<sub>A</sub>R<sub>B</sub>, O(CH<sub>2</sub>)<sub>1-4</sub>NR<sub>A</sub>R<sub>B</sub>, or NR<sub>2</sub>(CH<sub>2</sub>)<sub>1-4</sub>NR<sub>A</sub>R<sub>B</sub>;  
 O(CH<sub>2</sub>)<sub>1-4</sub>OR<sub>1</sub>, or NR<sub>2</sub>(CH<sub>2</sub>)<sub>1-4</sub>OR<sub>1</sub>;

15

R<sub>1</sub> is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (phenyl)C<sub>1-4</sub> alkyl, (phenyl)C<sub>3-4</sub> alkenyl, (phenyl)C<sub>3-4</sub> alkynyl, (C<sub>3-8</sub> cycloalkyl)-C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkenyl, or (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkynyl;

20

each of R<sub>2</sub> and R<sub>3</sub> is independently H, phenyl, C<sub>1-4</sub> alkyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl;

25

each of R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> is independently H, Cl, F, or Br;

$R_A$  is H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (aminosulfonyl)phenyl, [(aminosulfonyl)phenyl]C<sub>1-4</sub> alkyl, (aminosulfonyl)C<sub>1-6</sub> alkyl, (aminosulfonyl)C<sub>3-6</sub> cycloalkyl, or [(aminosulfonyl)C<sub>3-6</sub> cycloalkyl]C<sub>1-4</sub> alkyl;

$R_B$  is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or phenyl;

J is SR<sub>C</sub>, OR<sub>C</sub>, SO<sub>2</sub>R<sub>C</sub>, SOR<sub>C</sub>, SO<sub>2</sub>NR<sub>D</sub>R<sub>E</sub>, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, C<sub>5-8</sub> cycloalkenyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, -M'E'G', (heterocyclic radical)-M'E'-G', or (cycloalkyl)-M'E'-G';

15 M' is O, SO, SO<sub>2</sub>, NR<sub>E</sub>, (CO)NR<sub>E</sub>, NR<sub>E</sub>(CO), SO<sub>2</sub>NR<sub>E</sub>, NR<sub>E</sub>SO<sub>2</sub>, or CH<sub>2</sub>;

E' is absent (a covalent bond), (CH<sub>2</sub>)<sub>1-4</sub> or (CH<sub>2</sub>)<sub>m</sub>O(CH<sub>2</sub>)<sub>p</sub> where 1 ≤ (each of m and p independently) ≤ 3 and 2 ≤ (m + p) ≤ 4;

20 G' is OR<sub>3</sub>, SO<sub>2</sub>R<sub>C</sub>, or NR<sub>F</sub>R<sub>G</sub>; provided that where p = 1, then G' is H; each of R<sub>C</sub>, R<sub>D</sub>, R<sub>E</sub>, R<sub>F</sub> and R<sub>G</sub> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> heterocyclic radical, and phenyl; NR<sub>F</sub>R<sub>G</sub> and NR<sub>D</sub>R<sub>E</sub> can each also independently be selected from 25 morpholinyl, pyrazinyl, piperazinyl, pyrrolidinyl, or piperadinyl;

R<sub>10</sub> is H, C<sub>1-4</sub> alkyl, halo, NO<sub>2</sub>, or SO<sub>2</sub>NR<sub>H</sub>R<sub>I</sub>; and

R<sub>11</sub> is H, halo, or NO<sub>2</sub>;

wherein each hydrocarbon radical or heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, phenyl, hydroxy, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl,

5 alkynyl or phenyl is in turn optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxy, amino, and NO<sub>2</sub>;

or a pharmaceutically acceptable salt or C<sub>1-7</sub> ester thereof.

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2. A compound of claim 1, wherein R<sub>C</sub> is C<sub>1-2</sub> alkyl.

3. A compound of claim 1, wherein W is OH.

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4. A compound of claim 1, wherein W is NHOH.

5. A compound of claim 1, wherein W is NHO(cyclopropylmethyl).

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6. A compound of claim 1, wherein R<sub>10</sub> is methyl or chloro.

7. A compound of claim 1, where R<sub>11</sub> is fluoro.

8. A compound of claim 1, where R<sub>11</sub> is H.

25

9. A compound of claim 1, wherein J is trihalomethyl or methylthio.

10. A compound of claim 1, wherein J is 1,2,5-thiadiazol-3-yl.

11. A compound of claim 1, wherein J is SO<sub>2</sub>CH<sub>3</sub>.

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12. A compound of claim 1, wherein J is SOCH<sub>3</sub>.

13. A compound of claim 1, wherein J is C<sub>2-8</sub> alkynyl where the triple bond is between the carbon atoms alpha and beta to the phenyl group.

14. A compound of claim 1, wherein R<sub>1</sub> has at least one hydroxy 5 substituent.

15. A compound of claim 1, wherein R<sub>1</sub> is H, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, phenethyl, allyl, C<sub>3-5</sub> alkenyl, C<sub>3-5</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, (C<sub>3-5</sub> cycloalkyl)C<sub>1-2</sub> alkyl, or (C<sub>3-5</sub> heterocyclic radical)-10 C<sub>1-2</sub> alkyl.

16. A compound of claim 15, wherein R<sub>1</sub> is H or (C<sub>3-4</sub> cycloalkyl)-C<sub>1-2</sub> alkyl.

15 17. A compound of claim 1, wherein R<sub>2</sub> is H, methyl, C<sub>3-4</sub> alkynyl, C<sub>3-5</sub> cycloalkyl, or (C<sub>3-5</sub> cycloalkyl)methyl.

18. A compound of claim 1, wherein R<sub>A</sub> is H, methyl, ethyl, isobutyl, hydroxyethyl, hydroxypropyl, cyclopropylmethyl, cyclobutylmethyl, C<sub>2-4</sub> alkynyl, 20 phenyl, 2-piperidin-1-yl-ethyl, 2,3-dihydroxy-propyl, 3-[4-(2-hydroxyethyl)-piperazin-1-yl]-propyl, 2-pyrrolidin-1-yl-ethyl, or 2-diethylamino-ethyl; and R<sub>B</sub> is H; or where R<sub>B</sub> is methyl and R<sub>A</sub> is phenyl.

19. A compound of claim 1, wherein each of R<sub>4</sub> and R<sub>6</sub> is H, 25 and R<sub>5</sub> is F.

20. A compound of claim 1, wherein each of R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> is F.

21. A compound of claim 1, wherein each of R<sub>4</sub> and R<sub>5</sub> is F 30 and R<sub>6</sub> is Br.

22. A compound of claim 1, wherein R<sub>5</sub> is F.

23. A compound of claim 1, having the structure: 4-fluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 2-(4-methanesulfinyl-2-methyl-phenylamino)-4-nitro-benzoic acid; 3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 2-(2-methyl-4-methylsulfanyl-phenylamino)-4-nitro-benzoic acid; 3,4,5-trifluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 4-fluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4,5-trifluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 4-fluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 2-(4-methanesulfonyl-2-methyl-phenylamino)-4-nitro-benzoic acid; N-cyclopropylmethoxy-4-fluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-4-nitro-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-4-nitro-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-4-fluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide;

methanesulfonyl-2-methyl-phenylamino)-benzamide; or N-cyclopropylmethoxy-2-(4-methanesulfonyl-2-methyl-phenylamino)-4-nitro-benzamide.

24. A compound of claim 1, having the structure: 4-fluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; 5-bromo-3,4-difluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; 3,4-difluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-4-nitro-benzamide; 3,4,5-trifluoro-N-hydroxy-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; 3,4-difluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-hydroxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-4-nitro-benzamide; 8: 3,4,5-trifluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 4-fluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-bromo-3,4-difluoro-N-hydroxy-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; 15 3,4,5-trifluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; 4-fluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-bromo-3,4-difluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 3,4-difluoro-N-hydroxy-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; or N-hydroxy-2-(4-methanesulfonyl-2-methyl-phenylamino)-4-nitro-benzamide.

25. A compound of claim 1, having the structure: 3,4-difluoro-2-(4-imidazol-1-yl-2-methyl-phenylamino)-benzoic acid; N-cyclopropylmethoxy-3,4-difluoro-2-(4-imidazol-1-yl-2-methyl-phenylamino)-benzamide; 3,4-difluoro-N-hydroxy-2-(4-imidazol-1-yl-2-methyl-phenylamino)-benzamide; 3,4,5-trifluoro-2-(2-methyl-4-[1,2,5]thiadiazol-3-yl-phenylamino)-benzoic acid; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(2-methyl-4-[1,2,5]thiadiazol-3-yl-phenylamino)-benzamide; 3,4,5-trifluoro-N-hydroxy-2-(2-methyl-4-[1,2,5]thiadiazol-3-yl-phenylamino)-benzamide; 2-[4-(4-chloro-[1,2,5]thiadiazol-3-yl)-2-methyl-phenylamino]-3,4,5-trifluoro-benzoic acid; 2-[4-(4-chloro-[1,2,5]thiadiazol-3-yl)-2-methyl-phenylamino]-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-[4-(4-chloro-[1,2,5]thiadiazol-3-yl)-2-methyl-phenylamino]-

3,4,5-trifluoro-N-hydroxy-benzamide; 2-[4-[4-(2-dimethylamino-ethoxy)-  
[1,2,5]thiadiazol-3-yl]-2-methyl-phenylamino}-3,4,5-trifluoro-benzoic acid; N-  
cyclopropylmethoxy-3,4,5-trifluoro-2-{2-methyl-4-[4-(2-piperidin-1-yl-ethoxy)-  
[1,2,5]thiadiazol-3-yl]-phenylamino}-benzamide; or 3,4,5-trifluoro-N-hydroxy-2-{2-  
5 methyl-4-[4-(2-morpholin-4-yl-ethoxy)-[1,2,5]thiadiazol-3-yl]-phenylamino}-  
benzamide.

26. The compound of claim 1, having a structure selected from:

5-bromo-2-(2-chloro-4-methylsulfanyl-phenylamino)-3,4-difluoro-benzoic acid; 2-  
10 (2-chloro-4-methanesulfinyl-phenylamino)-3,4-difluoro-benzoic acid;  
2-(2-chloro-4-methanesulfonyl-phenylamino)-3,4,5-trifluoro-benzoic acid;  
2-(2-chloro-methylsulfanyl-phenylamino)-3,4-difluoro-benzoic acid;  
5-bromo-2-(2-chloro-4-methanesulfonyl-phenylamino)-3,4-difluoro-benzoic acid;  
2-(2-Chloro-4-methanesulfonyl-phenylamino)-3,4-difluoro-benzoic acid;  
15 5-bromo-2-(2-chloro-4-methylsulfanyl-phenylamino)-N-cyclopropylmethoxy-3,4-  
difluoro-benzamide; 2-(2-chloro-4-methanesulfinyl-phenylamino)-N-  
cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methanesulfonyl-  
phenylamino)- N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-  
methylsulfanyl-phenylamino)- N-cyclopropylmethoxy-3,4-difluoro-benzamide;  
20 2-(2-chloro-4-methanesulfinyl-phenylamino)- N-cyclopropylmethoxy-3,4,5-  
trifluoro-benzamide; 5-bromo-2-(2-chloro-4-methanesulfonyl-phenylamino)-N-  
cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methylsulfanyl-  
phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-  
methanesulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;  
25 2-[2-chloro 4-(3H-imidazol-1-yl)-phenylamino]-N-cyclopropylmethoxy-3,4-difluoro-  
benzamide; 2-(2-chloro-4-[1,2,5]thiadiazol-3-yl-phenylamino)-N-  
cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-[4-(2-chloro-4-chloro-  
[1,2,5]thiadiazol-3-yl)-phenylamino]-3,4,5-trifluoro-benzoic acid; 2-[2-chloro-4-(4-  
chloro-[1,2,5]thiadiazol-3-yl)-phenylamino]-N-cyclopropylmethoxy-3,4,5-trifluoro-  
30 benzamide; 2-{4-[4-(2-dimethylamino-ethoxy)-[1,2,5]thiadiazol-3-yl]-2-methyl-  
phenylamino}-3,4,5-trifluoro-benzoic acid; 2-{2-chloro-4-[4-(2-piperidin-1-yl-

ethoxy)-[1,2,5]thiadiazol-3-yl]-phenylamino}-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide.

27. The compound of claim 1, having a structure selected from:

5 2-(4-Ethynyl-2-methyl-phenylamino)-4-fluoro-benzoic acid; 5-Bromo-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzamide; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-4-nitro-Benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(4-Ethynyl-2-methyl-phenylamino)-4-nitro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-benzamide; 4-Fluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-Bromo-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-4-fluoro-benzamide; 5-Bromo-N-cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-N-hydroxy-4-nitro-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-4-fluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-4-fluoro-benzamide; and 4-Fluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide.

28. The compound of claim 1, having a structure selected from:

25 2-(2-Chloro-4-ethynyl-phenylamino)-4-fluoro-benzoic acid; 5-Bromo-2-(2-chloro-4-ethynyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-4-nitro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)- N-hydroxy-3,4,5-trifluoro- benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(4-Ethynyl-2-chloro-phenylamino)-4-nitro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-Cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-methanesulfinyl-

phenylamino)- 4-fluoro-N-hydroxy-benzamide; 5-Bromo-2-(4-ethynyl-2-chloro-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-4-fluoro-benzamide; 5-Bromo-2-(2-chloro-4-ethynyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(4-Ethynyl-2-chloro-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; 2-(4-Ethynyl-2-chloro-phenylamino)-N-hydroxy-4-nitro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-4-fluoro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-4-fluoro-benzamide; 2-(2-Chloro-4-methanesulfinyl-phenylamino)- 4-fluoro-N-hydroxy-benzamide; and 2-(2-chloro-4-imidazol-1-yl-phenylamino)- 3,4-Difluoro-benzoic acid.

29. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically-acceptable carrier.

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30. A method for treating a proliferative disease, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

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31. A method of claim 30, wherein said proliferative disease is selected from psoriasis, restenosis, autoimmune disease, and atherosclerosis.

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32. A method for treating cancer, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

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33. A method of claim 32, wherein said cancer is MEK-related.

34. A method of claim 32, wherein said cancer is colorectal, cervical, breast, ovarian, brain, acute leukemia, gastric, non-small cell lung, pancreatic, prostatic, or renal.

35. A method for treating, or ameliorating the sequelae of, a stroke, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of

5 claim 1.

36. A method for treating, or ameliorating the sequelae of, heart failure, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of

10 claim 1.

37. A method for treating or reducing the symptoms of xenograft rejection, said method comprising administering to a cell transplant, limb transplant, skin transplant, an organ transplant or bone marrow transplant patient

15 a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

38. A method for treating osteoarthritis, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective

20 amount of a composition comprising a compound of claim 1.

39. A method for treating rheumatoid arthritis, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

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40. A method for treating cystic fibrosis, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

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41. A method for treating hepatomegaly, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

42. A method for treating cardiomegaly, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

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43. A method for treating Alzheimer's disease, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

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44. A method for treating a complication of diabetes, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

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45. A method for treating septic shock, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

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46. A method for treating a viral infection, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

47. A method of claim 46, wherein said viral infection is a HIV infection.

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48. A method for treating cancer, said method comprising  
(a) administering to a patient in need of such treatment, a pharmaceutically-effective amount of a composition comprising a compound of claim 1; and  
(b) administering a therapy selected from radiation therapy and chemotherapy.

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49. A method of claim 48, wherein said chemotherapy comprises a mitotic inhibitor.

50. A method of claim 49, wherein said mitotic inhibitor is selected from paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine.

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09/889106

**Associate Power of Attorney Or Agent (37 CFR 1.34)  
(For Representation Related To A Patent Application)**

Docket No.  
5940-01-SMH

In Re Application Of: Stephen Douglas Barrett, et al.

Serial No.	Filing Date	Examiner	Group Art
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Invention: 4' Heteroaryl Diarylamines

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Dated: 7/11/01

I certify that this document is being deposited on  
July 11, 2001 with the U.S. Postal Service as first  
class mail under 37 C.F.R. 1.8 and is addressed to the  
Assistant Commissioner for Patents, Washington, D.C.  
20231.

*Signature of Person Mailing Correspondence*

Linda A. Zerby

*Typed or Printed Name of Person Mailing Correspondence*

**COMBINED DECLARATION FOR PATENT  
APPLICATION AND POWER OF ATTORNEY  
(Includes Reference to PCT International Applications)**

Attorney's Docket Number

5940-01-EDS

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**4' HETEROARYL DIARYLAMINES**

the specification of which (check only one item below):

is attached hereto.  
 was filed as United States application

Serial No

on

and was amended

on \_\_\_\_\_ (if applicable).

was filed as PCT international application  
Number PCT/US 99/30491  
on December 21, 1999  
and was amended  
on \_\_\_\_\_ (if applicable).

Thereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under United States Code 37 CFR § 119(a-d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a), or of any PCT international application which designated at least one country other than the United States of America listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or any PCT international application having a filing date before that of the application of which priority is claimed:

**Prior Foreign Application(s)**

APPLICATION NUMBER	COUNTRY (if PCT, indicate "PCT")	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
			<input type="checkbox"/> yes <input type="checkbox"/> no
			<input type="checkbox"/> yes <input type="checkbox"/> no

**I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:**

APPLICATION NUMBER	DATE OF FILING
60/115,876	13 January 1999
60/122,583	02 March 1999

Combined Declaration For Patent Application and Power of Attorney (Continued)  
(Includes Reference to PCT International Applications)

Attorney Docket Number

5940-01-EDS

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information which is material to patentability as defined in 37 CFR, §1.56(a) which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

**PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:**

U S APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO	PCT FILING DATE	U S SERIAL NUMBERS ASSIGNED (if any)		
PCT/US99/30491	December 21, 1999		X	

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number): Charles W. Almer, III (Reg. No. 36,731), Elizabeth Anderson (Reg. No. 31,585), Charles W. Ashbrook (Reg. No. 27,610), Michael J. Atkins (Reg. No. 35,431), Jean B. Barish (Reg. No. 34,118), Evan J. Federman (Reg. No. 37,060), M. Andrea Ryan (Reg. No. 28,649), Evelyn D. Shen (Reg. No. 39,834), Francis J. Tinney (Reg. No. 33,069), Linda Vag (Reg. No. 32,071)

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	Citizenship	: United States of America
	Post Office Address	: Same

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.